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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

EDITORS

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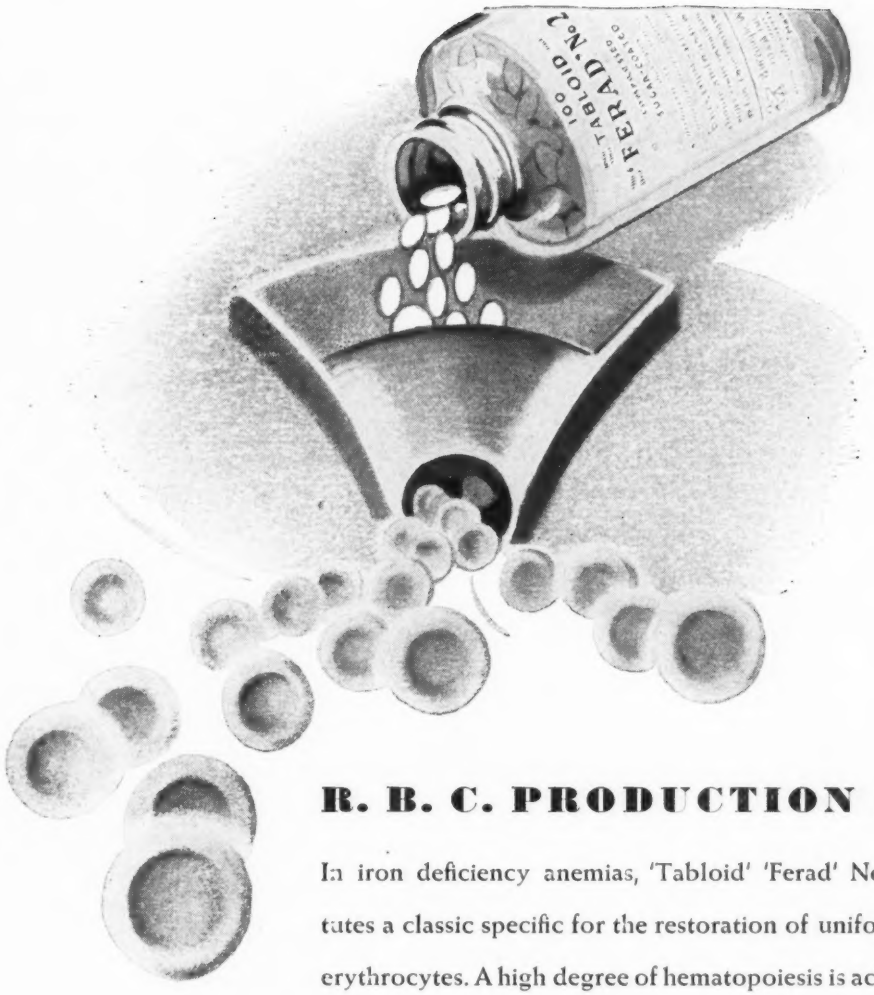

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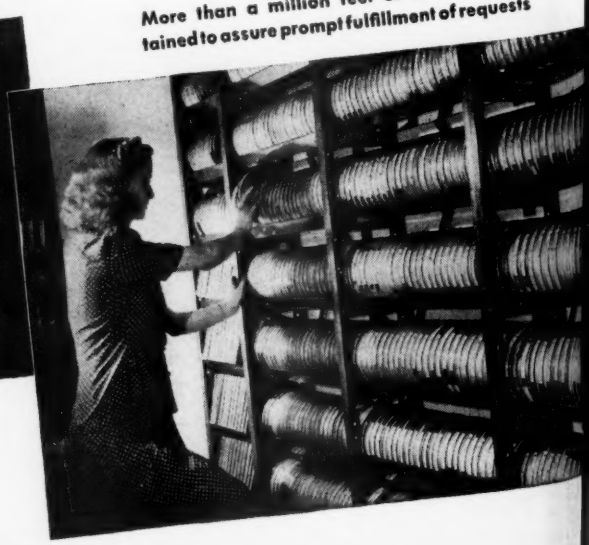

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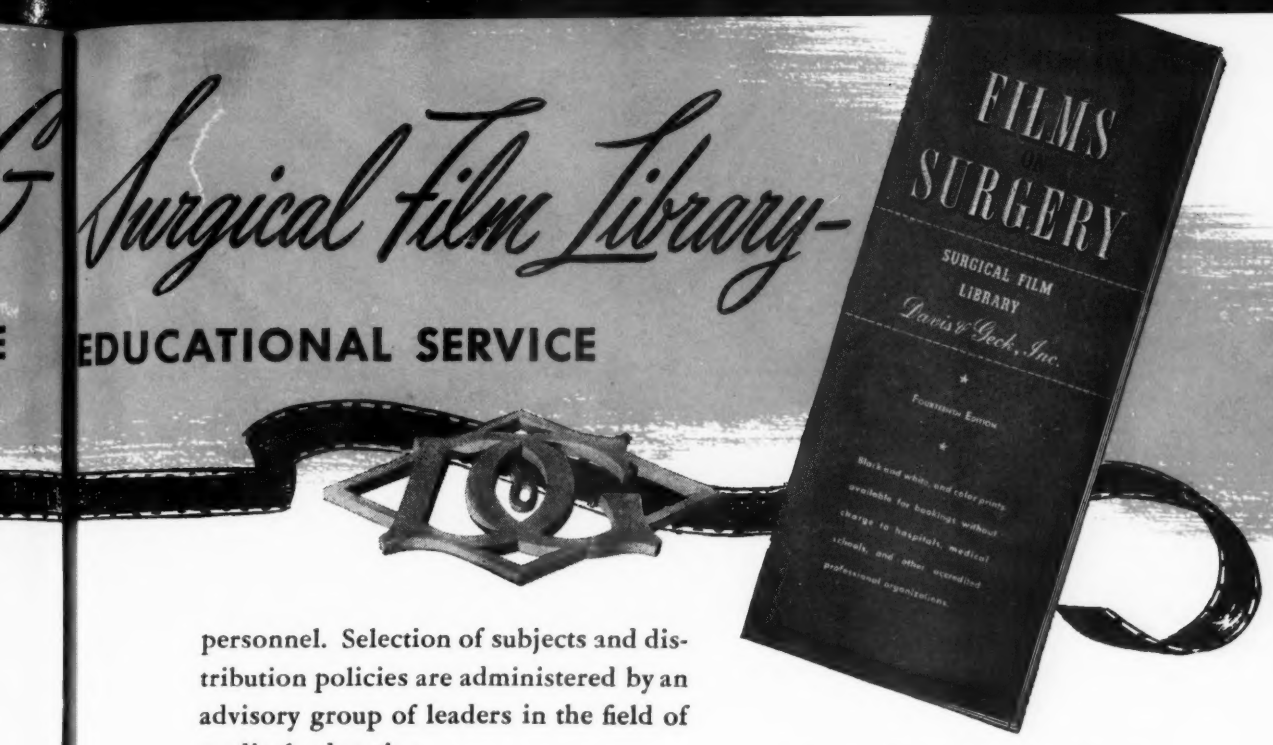
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*Kramer, G. B., and Sedwitz, S. H.: Ceepryn: clinical and bacteriological studies, Am. J. Surg. 63:240-245 (Feb.) 1944

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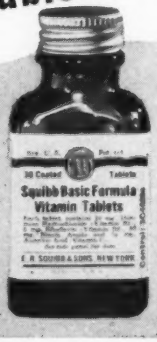

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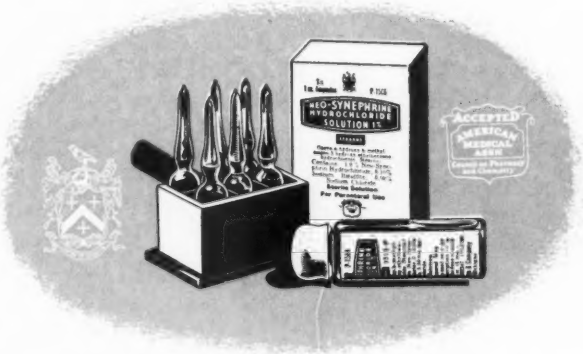

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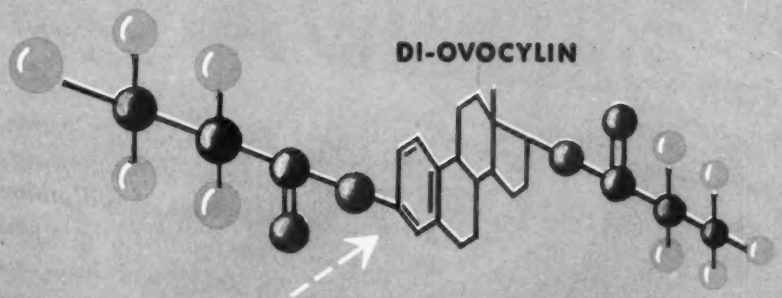

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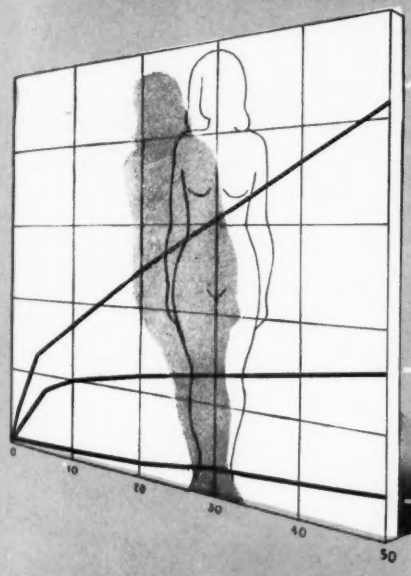

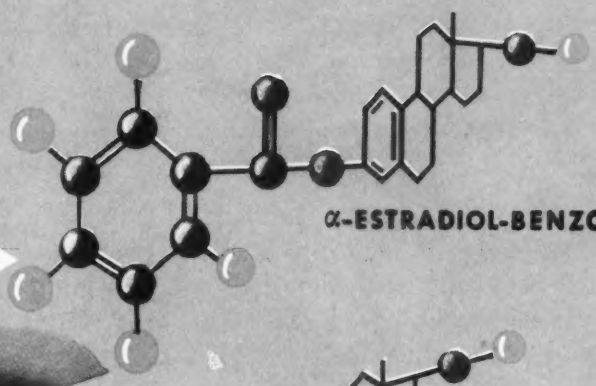

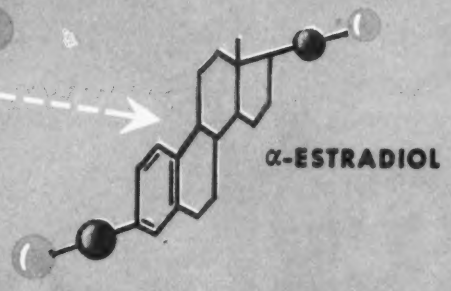

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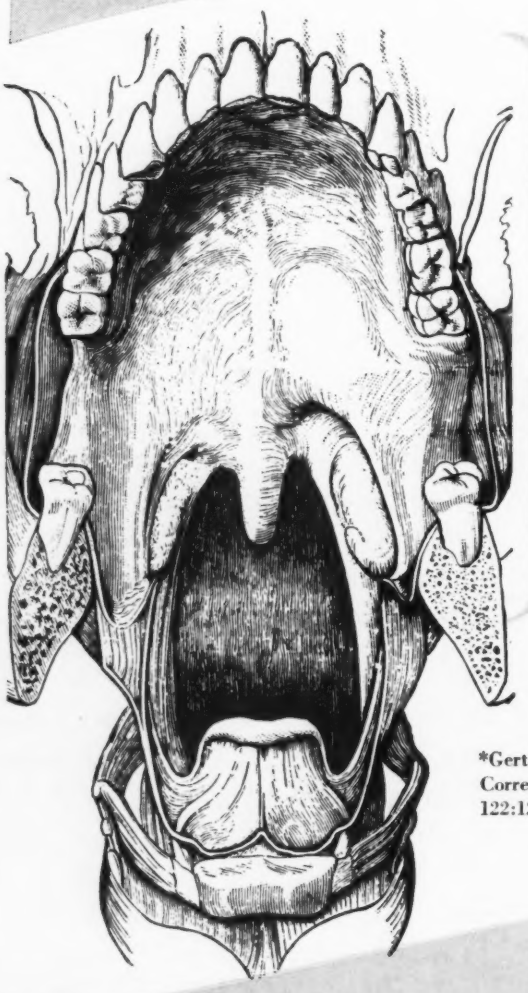

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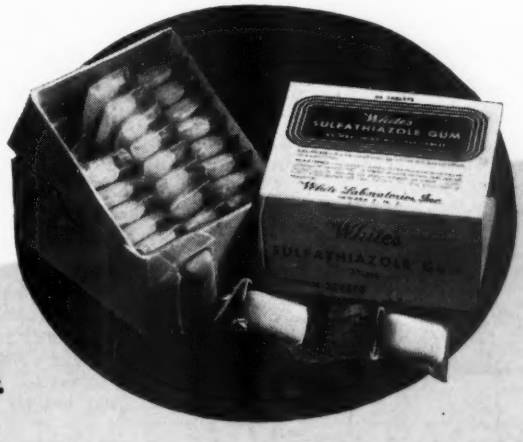

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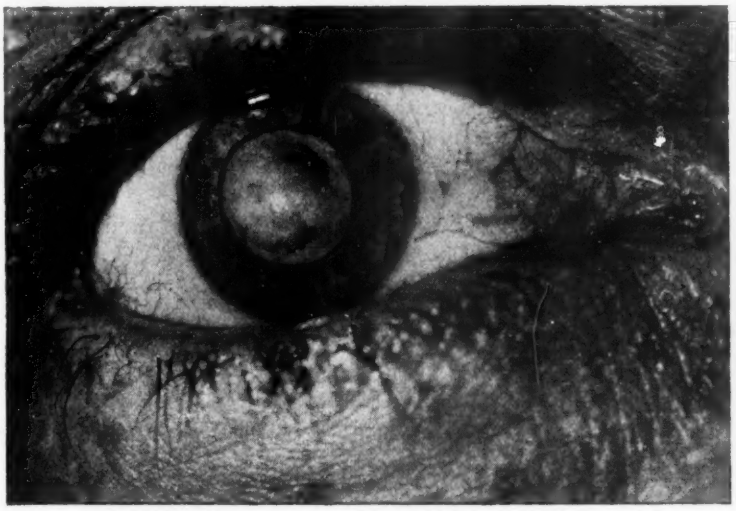

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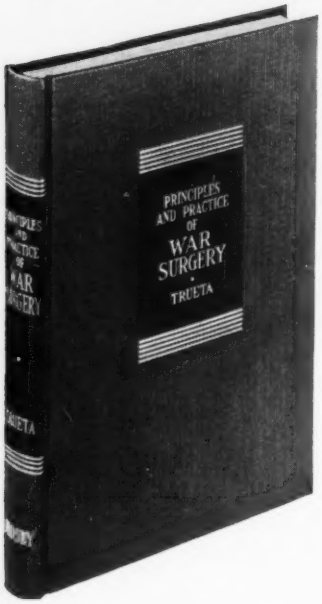

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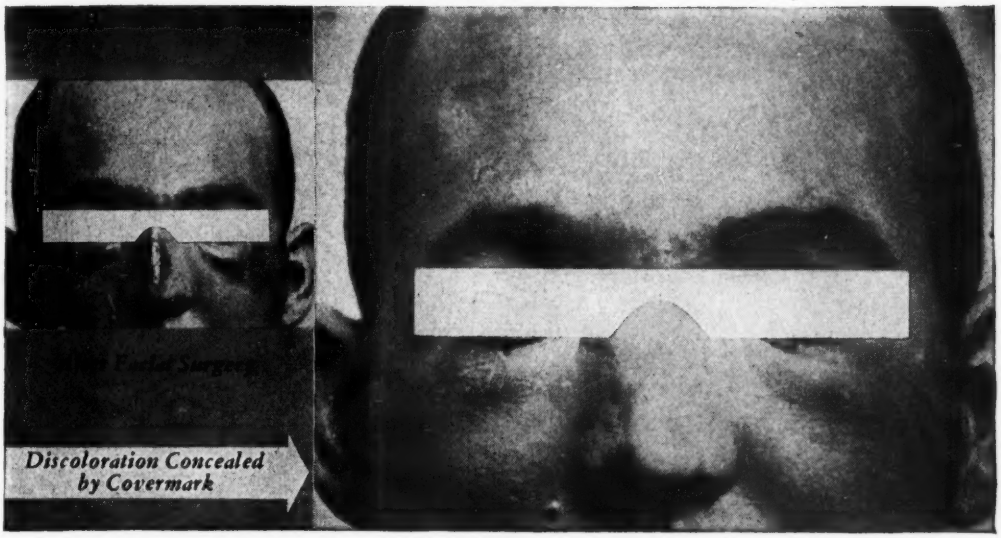

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SURGERY

VOL. 16 SEPTEMBER, 1944 No. 3

Original Communications

MYOBLASTOMA*

CHESTER W. HOWE, M.D., BOSTON, MASS., AND
LIEUTENANT COMMANDER SHIELDS WARREN, MEDICAL CORPS, U.S.N.R.
(From the Pondville Hospital, Massachusetts Department of Public Health and the Laboratory of Pathology of the Harvard Cancer Commission)

ONE of the less well-recognized tumors is the myoblastoma, whose type cell is the primitive precursor of striated muscle. Within the past few years we have encountered ten cases, five of which showed definite malignant properties; three of the latter metastasized to the lungs.

Since knowledge of the clinical behavior of these tumors is still scanty, it seems worth while to review that knowledge and to present the clinical and pathologic features exhibited by these cases. The tumor was first described by Abrikossoff[1] in 1926 as a tumor of myoblasts, occurring chiefly in relation to striated muscle. Some of the cases, as those of Keynes[30] and Dewey,[14] have been reported as rhabdomyoma. In 1933 Klemperer[32] reviewed the subject and collected forty-four cases, adding six new ones from his own material. Gray and Gruenfeld,[24] in 1937, published a topographic grouping of the cases then known and added five new ones, bringing the total to seventy-seven. In 1943, Horn and Stout[26] reported two cases and mentioned twenty-seven more in their material.

Myoblastoma must be differentiated from other primitive tumors of mesenchymal type on the one hand and from rhabdomyoma and rhabdomyosarcoma on the other hand. The two chief types of readily recognized striated muscle tumors are those occurring in voluntary and those occurring in cardiac muscle. Those arising from voluntary

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muscle and those striated muscle elements in teratoid tumors usually present elongate to banjo-shaped cells, with often longitudinal striations and sometimes cross striations. The type occurring in cardiac muscle is usually made up, at least in part, of very large,[34] rounded cells of so-called spider-web type with the striations arranged somewhat concentrically. The cardiac tumors are almost all congenital and benign.

The characteristic cell in myoblastoma is large, pale, polyhedral, and granular, frequently arranged in pseudo-alveolar fashion, although lumina are not formed (Fig. 1). Not infrequently, ribbonlike or irregular syncytial masses may occur. In both of these types of cells the cytoplasm is somewhat granular and resembles that of primitive myoblasts. Rarely, a few cross striations may be present (Abrikossoff[1, 2] reported them in two of his cases). The cytoplasm tends to be acidophilic and sometimes is vacuolated. It is quite possible, if one does

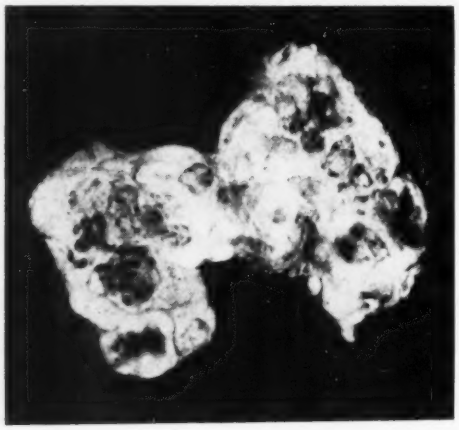

Fig. 1.—Gross specimen of primary tumor, Case 1.

not carry out stains for lipoid, to mistake them for xanthoma cells. The nuclei are small as contrasted with the cytoplasm and vary a little in size; they may be vacuolated (Fig. 2). Mitotic figures are rare. Frequently cells contain multiple nuclei. A delicate connective tissue stroma supports either single cells or groups of cells. Often a definite capsule is present, but if it is absent, the tumor cells blend almost imperceptibly with the adjacent striated muscle.

Abrikossoff[1] originally distinguished four varieties of muscle tumor under the heading of myoblastoma: (1) Tumors composed of myoblasts completely devoid of striations; the pure myoblastoma. (2) Tumors with myoblasts similar to type 1 but showing infrequent longitudinal or cross striations or both, only imperfectly developed in the margins of cells. (3) Tumors with hypertrophic myoblasts, including some of great size (40 to 160 micra in length), frequently multinucleated and of syncytial type. Striation may be present in some,

especially in the peripheral zone of cytoplasm, but is absent from many. (4) Atypical myoblastic sarcoma; a polymorphous-celled tumor, in some areas frankly sarcomatous, in others showing more highly differentiated cells with well-defined longitudinal and cross striation.

In our opinion, Abrikossoff's[1] Group 4 cases are better included with the rhabdomyosarcomas and we have so diagnosed our own examples of the group. To avoid confusion in tabulating the reported cases, we have included those previously recorded as meeting the criteria for Abrikossoff's Group 4 as well as those falling in his first three groups.

Fig. 2.—Pleural metastases of myoblastoma, Case 1.

It is easy to determine the nature of this tumor when it occurs in contact with striated muscle and when scattered transitional cell forms exist. Such transition cells have been reported by Gray and Gruenfeld[24] (tumors of tongue) and by Grayzel and Friedman[25] in a tumor of the thoracic wall. While some authors[13, 15] illustrated apparent transition of the granular cells into striated cells, others[32, 42, 48] believe that these are probably erroneous interpretations. As has been pointed out by Klinge,[33] the occurrence of the tumor in regions where no striated muscles appear can be explained only on a dysontogenetic basis. It has been suggested[42, 47] that following trauma to striated muscle, granular degeneration might occur and excessive regeneration taking place in such injured fibers might lead to the development of neoplastic qualities.

The tumor is usually first noted as a small, yielding, nontender mass, often only 1 cm. or more in diameter. On section it is grayish pink

or whitish and as a rule fairly clearly demarcated, although it occasionally shows no definite border. Ulceration is rare and, indeed, there may be hyperplastic or neoplastic response of the overlying skin or mucous membrane. The great majority of these tumors are benign, but we, as others, have encountered malignant ones, which will be discussed later in this communication.

CASE HISTORIES

CASE 1.—M. V., a 36-year-old white American housewife entered Pondville Hospital, March 27, 1941, complaining of aching and swelling of the upper left arm of two and one-half months' duration. Examination showed a hard, movable, fusiform mass 4 cm. in diameter on the anterior aspect of the left shoulder at the level of the surgical neck of the humerus.

May 31, 1941, the mass was excised taking the overlying attached skin and subcutaneous tissue and some of the deltoid muscle fibers. Pathologic report on the specimen was "myoblastoma" (Fig. 1).

From August to December, 1941, she worked in an ammunition factory, and in common with other workers there developed what she called a "tetryl cold" and experienced nasal discharge, nosebleeds, headaches, yellow skin discoloration (perspiration stained clothes yellow), and a mild attack of diarrhea. At this time she experienced pain in the right shoulder.

Jan. 8, 1942, she appeared at Pondville Hospital Out Patient Clinic complaining of pain in the right shoulder, shin, and hip. Two months previously she had first noted an enlarging tumor mass in the right upper arm. Examination at this time showed a well-healed, postoperative scar with no recurrence on the left. In the right mid-humeral region there was a fusiform hard mass 5 cm. in diameter fixed to the underlying bone. Also, just medial to the right anterior superior spine of the ilium there was an indefinitely outlined, hard mass roughly 8 cm. in diameter, fixed and slightly tender. Skeletal x-rays showed slight rarefaction in the right humerus not typical of metastatic disease. No other bone pathology was found. The patient was given a course of deep x-ray therapy consisting of 2,000 r to the right humerus and 2,000 r to the right iliac crest region.

Feb. 5, 1942, she reappeared in the outpatient department on a stretcher with obvious severe pain in her right shoulder, right hip, and back. X-rays at this time showed metastatic disease in the fifth dorsal vertebra and in the left pubic bone. She was treated by deep x-ray therapy to the extent of 1,800 r distributed to the various painful areas.

During mid-February she developed numbness along the lower jaw on the right side, progressing to severe pain at the tip of the chin. X-ray pictures of the foramen ovale showed no evidence of bone metastases.

Blood studies showed a progressive anemia (normocytic) and a low white count. A bone marrow biopsy was essentially negative.

March 14, 1942, a fixed mass of fused lymph nodes 3 cm. in diameter was removed from high in the left axilla and was proved pathologically to be metastatic myoblastoma.

The patient had a constant temperature of about 100° F. and the pulse averaged 115. The pain increased and required large doses of morphine. X-ray checkup pictures showed advancing disease in the thoracic spine, left scapula, and left innominate bone. Additional x-ray therapy was given with only partial relief of pain. Extensive blood chemistry studies were carried out which served to throw no light on the nature of the disease. The pain increased, appetite failed, and the patient became bedridden. There was marked weight loss and she died on April 28, 1942.

Autopsy showed primary myoblastoma of the left deltoid region with multiple metastases to bones, pleura, lungs, axillary and tracheobronchial lymph nodes, liver, and adrenals. There was bilateral hydrothorax and the external surfaces of the lungs were studded with tumorous nodules (Fig. 2).

CASE 2.—O. S., a 64-year-old man, inmate of the Taunton State Mental Hospital, was admitted to Pondville Hospital for treatment of a small tumor on his tongue. Due to the patient's mental status, no history was obtained except the fact that he was a heavy pipe smoker.

Examination showed a granular lesion 7 mm. in diameter, firm and whitish, on the left side of the tip of the tongue. The teeth were ragged and foul. It was thought at the time that the lesion was of dental etiology. There were no palpable cervical nodes.

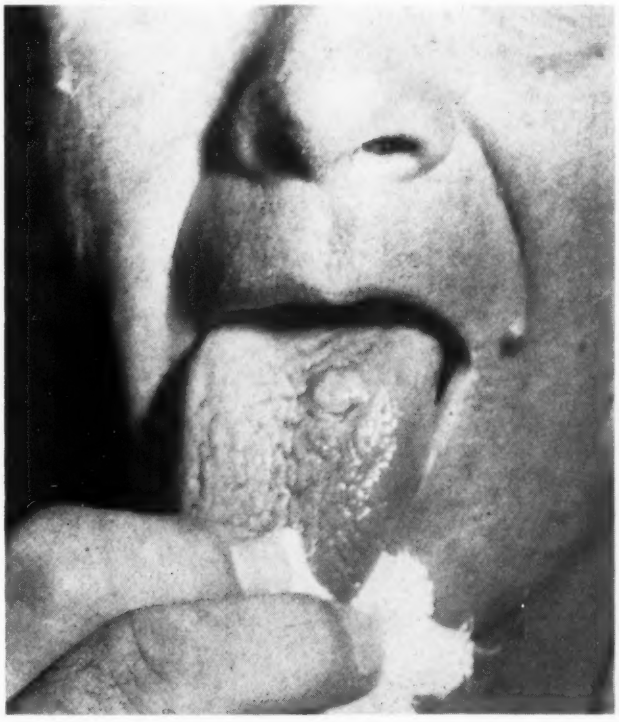

Fig. 3.—Myoblastoma of tongue.

July 1, 1940, partial glossectomy was done. The tumor of the removed specimen was 8 by 7 by 4 mm. and grayish white on cut section. Microscopically the picture was one of a type 2 myoblastoma.

The patient had an uneventful convalescence, and when last seen two years after operation was free from disease.

CASE 3.—L. F., a 17-ye- old, single female, was first seen at the Westfield State Sanatorium in April, 1941, having had a previous excision of a tumor of the left buttock, elsewhere. She had a history of being in an automobile accident February, 1941, at which time she had received numerous contusions and abrasions to the body. Following this she complained of low back pain and was kept in bed four or five days. During this time she began to complain of a tender, painful swelling in the left buttock about the size of a small hen's egg. This grew and became more tender as a result of lying on it.

When first seen at Westfield, there was a scar 3 cm. in length just lateral to the crest of the ilium. The zone of the previous excision was widely excised, and the pathologic report was hemangioendothelioma. (These microscopic sections were not available to us for review.)

In January, 1942, on a follow-up visit, an egg-sized mass was found at the junction of the upper and middle thirds of the incision. This mass was slightly movable. It was again widely excised, and the pathologic report was myoblastoma (Fig. 5).

She was given x-ray treatment, totaling 2,500 r, directed to the tumor site in the left gluteal region.

She was followed regularly at the Westfield Out Patient Department, the last follow-up visit being in August, 1943, at which time there was no evidence of recurrent disease. She has had no menstrual period since the x-ray treatment and is suffering from hot flashes.

CASE 4.—A. K., an 81-year-old man was admitted to the Lowell General Hospital complaining of a tumor on the outer aspect of the lower part of the left thigh. He gave a history of having had a tumor excised from this area previously, June 12, 1941. Examination showed an ovoid tumor 6.2 cm. in diameter centering in the scar of the previous excision. Operative note: Under novocain anesthesia the old scar and tumor were excised. The tumor was somewhat adherent to the underlying fascia but was separated from it without difficulty, leaving a smooth clean base. The wound was closed with interrupted mattress silk sutures. The specimen consisted of the skin scar tissue with an ovoid, flesh colored tumor 6.2 cm. in diameter attached. The tumor consisted of an outer solid grayish-white zone and an inner soft degenerated zone. The pathologic report was myoblastoma. When last seen, approximately one year following excision, there was no evidence of recurrence.

CASE 5.—E. P., a 24-year-old male laborer, was admitted to Pondville Hospital, Dec. 11, 1941, for excision of a tumor on the left hand, noted two years previously on the palm over the flexor tendon of the index finger, which had gradually increased in size to become 2 cm. in diameter. A second smaller tumor appeared adjacent to it. Gradually these tumors became painful and caused contraction of the index finger.

Nov. 11, 1941, these masses were excised by his physician and diagnosed myoblastoma, malignant.

The examination on entry showed an enlarged right tonsil, cervical, axillary, and inguinal adenopathy, bilateral epitrochlear adenopathy, and a scar 7 cm. in length along the thenar eminence of the left hand.

Blood studies were within normal limits, and the serology was negative.

The epitrochlear node was excised for biopsy and proved to be hyperplastic. A roentgenogram of the chest was negative. The patient was discharged at his own request but delayed in returning. When he did return, there was increased thickening in the scar with a nodule 2 cm. in diameter at one end. The cervical, axillary, and inguinal adenopathy remained unchanged.

Jan. 26, 1942, re-excision of the tumor was done (Fig. 4). Since it was impossible to remove all the tumor by local excision, permission for an amputation was obtained, and Feb. 10, 1942, a partial amputation of the left hand, leaving the lateral two fingers, was done. Sections of this specimen revealed tumor at the margin of the incision. The wound healed by first intention. The left axillary nodes increased in size and number.

Feb. 24, 1942, the patient had an amputation of the lower one-third of the forearm with epitrochlear and axillary dissection. Fifty-two lymph nodes were

Fig. 4.—Recurrent tumor, Case 5.

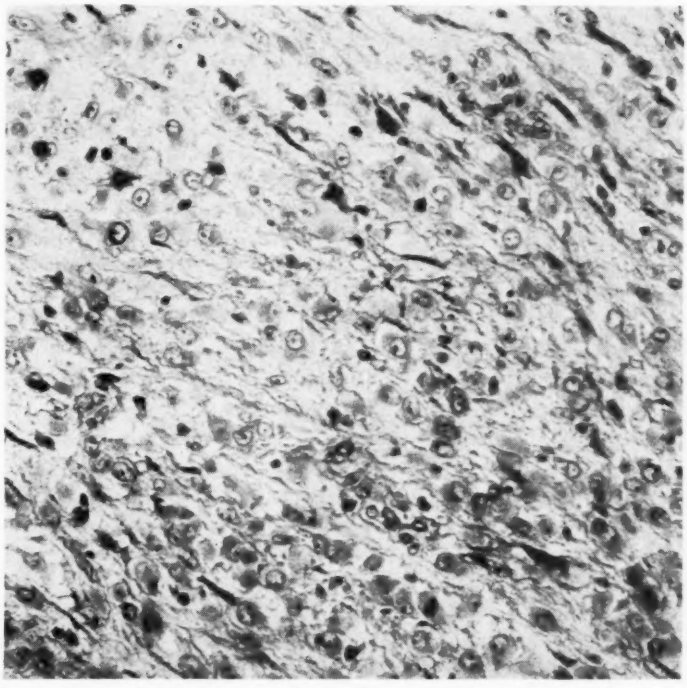

Fig. 5.—Myoblastoma, type 2 (Case 3). This field shows chiefly type 1 or granular cells. Phosphotungstic acid hematoxylin stain (×290).

removed with the dissection, all of which showed hyperplasia but no evidence of tumor. The removed specimens showed firm, gray tissue in the scar. The overlying epithelium was normal. There were clumps of polyhedral cells with foamy cytoplasm and few mitoses. Some of the cells were in syncytial strands.

Five months later there was neither recurrence nor metastasis.

CASE 6.—A. K., a 52-year-old white married woman, struck her right thigh against a table and the following morning developed marked swelling at the site of the trauma. During the next few weeks a large, soft, fungating tumor appeared over the same area. This was thought to be a broken-down hematoma and it was opened by her physician releasing much bloody material. A biopsy was submitted to the Tumor Diagnosis Service and a diagnosis of myoblastoma was made. Six weeks later the patient was brought to the Huntington Hospital by her physician. At that time examination showed a tumor 10 cm. in diameter in the outer aspect of the central part of the right thigh extending deeply into the subcutaneous tissues with a fungating mass 4 cm. in diameter breaking through the skin. There were no palpable inguinal lymph nodes. X-ray showed a large infiltrating, soft tissue tumor occupying one-half of the outer aspect of the right thigh. An amputation was advised, but the patient refused both this and local excision. She returned home to her physician, and a course of deep x-ray therapy (dosage not available) was given, followed by regression of the tumor. An area of marked radiation reaction measuring 15 by 20 cm. persisted.

In November, 1937, a roentgenogram of the chest showed a small shadow in the right upper lobe which continued to enlarge on repeated examinations in spite of deep x-ray therapy. Information was received that the patient died on April 1, 1938, with lung metastases. The local lesion of the thigh was completely healed and the patient had previously been able to walk about.

CASE 7.—C. L., a 71-year-old white man entered the Huntington Memorial Hospital Oct. 14, 1941. He stated that he had noticed a small rough lesion on the inside of his right cheek for some time and that five weeks previously, it had suddenly developed into a rapidly enlarging tumor. Examination on entry showed him to be edentulous and wearing an upper and lower plate. There was a rubbery, pedunculated growth measuring 2 by 3 cm. springing from the right buccal mucosa 1 cm. inside the right commissure. It appeared very vascular and was oozing bright red fluid. There was some roughening and granulation over a small area just posterior to the site of the tumor. A firm node 1 cm. in diameter was palpable in the right submaxillary triangle adjacent to the border of the mandible.

Examination Oct. 28, 1941, under trigeminal block anesthesia showed that the lesion was larger than it had first appeared, was pedunculated and stony hard. The tumor, with a wide margin of normal tissue, was removed by block dissection.

The specimen consisted of a mass of tissue measuring 4.5 by 3.5 by 2.5 cm. and was necrotic on one surface where it showed evidence of hemorrhage. On cut section tissue was firm and gray. A diagnosis of myoblastoma was made on microscopic section.

Nov. 15, 1941, a right supra-omohyoid neck dissection was done. The specimen consisted of a mass of fibrofatty tissue measuring 5.0 by 4.5 by 3.5 cm. On section one enlarged, homogeneous, cellular gray lymph node adjacent to a piece of salivary gland was found. The microscopic diagnosis was myoblastoma metastatic to one lymph node (Fig. 6).

Dec. 2, 1941, a recurrence of tumor 1 cm. in diameter was noted at the operative site. Biopsy showed recurrent myoblastoma. The patient was advised to have another excision. He did not appear again until April, 1942, at which time he was admitted to the Massachusetts General Hospital. He had no therapy in

the interim and there was a large, partly fluctuant metastatic mass extending from the right mandible to the clavicle. There was no regression following 2,100 r of deep x-ray therapy, and it was decided that the disease was too advanced to warrant further therapy. April 25, 1942, roentgenograms of the chest showed metastases to the hilar lymph nodes. The patient was discharged for terminal care and word was received that he died Aug. 3, 1942.

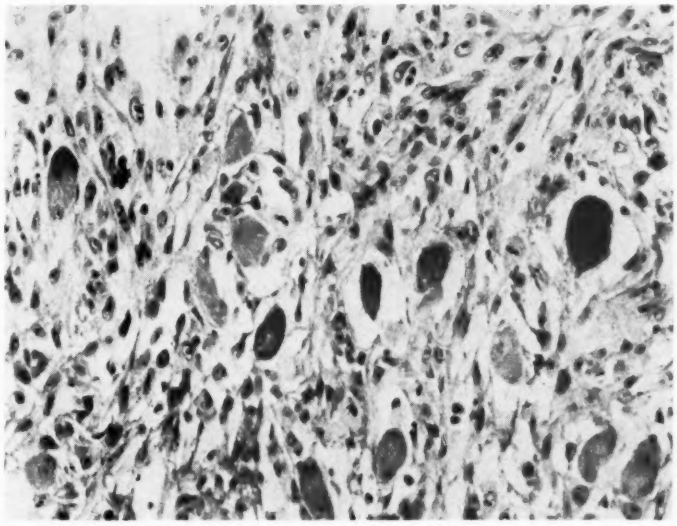

Fig. 6.—Myoblastoma, type 3 (Case 7). Note invasion of striated muscle. Phosphotungstic acid hematoxylin stain (×310).

Case 8.—W. G., a man 65 years of age, entered the Huntington Hospital complaining of a sore right chest. Six weeks previously, he had struck his right elbow severely; four and one-half weeks previously a swelling appeared in the right chest, which was poulticed for two weeks and then lanced with the escape of a considerable amount of "pus." On entry the patient showed a raised lobulated mass, ulcerated and necrotic, over the right pectoral region. This mass measured 20 by 12 by 6 cm. The peripheral nodules were moderately firm and made up of dull white tissue, whereas externally the tumor mass was dull grayish purple and necrotic. The patient died soon after entry. An autopsy showed that the tumor infiltrated and replaced a large portion of the pectoral muscle and invaded the costochondral junctions of the third and fourth ribs. The parietal pleura was not penetrated; no evidence of metastases was found. Microscopically, the tumor showed many tumor giant cells and was classified as a myoblastoma, Abrikossoff type 3.

Case 9.—Little information is available in this case. The tumor was sent to the Warren Museum of the Harvard Medical School by the late Dr. D. F. Jones in 1928 and was exhibited as a gross specimen of sarcoma. Through the courtesy of the curator, Dr. M. M. Canavan, we were able to study this tumor, which proved to be a myoblastoma, type 2. It presented itself as a spherical gray mass, 9 cm. in diameter, embedded in the gluteal muscles. While well demarcated, it was not encapsulated. Owing to the fixation, its consistency could not be determined, but apparently was about that of the muscle. The cut surface was fairly uniform, but indefinitely fibrillar.

Case 10.—H. H. This case is represented only by a slide found in the files of the Massachusetts State Tumor Diagnosis Service of a specimen submitted in

1925. No clinical information is available, other than that the tumor occurred in the left thigh of a man 81 years of age. The slide, diagnosed in 1925 as fibrosarcoma, shows a myoblastoma, type 3.

ANALYSIS OF CASES

The following analysis is based on the 44 cases collected by Klemperer,[32] 104 additional cases collected from the literature, regarded as meeting our criteria and summarized in Table I, and 10 cases, the tissues from which were studied in our laboratories (Table II).

Age.—The age distribution is not significant, as can be seen from Table I. One congenital tumor was found.

Duration.—Since most of the tumors are small when first noted, accurate data as to duration are almost impossible to obtain. However, of 50 cases with information regarding duration, 31 per cent of the benign lesions had been noticed for six months or less, as against 75 per cent of the malignant lesions (Table III).

Sex.—No significant variation in sex distribution was noted among the group.

Topography.—Data as to the location of the tumors are available in 158 cases (Table IV). Eighty-nine cases occurred in the upper digestive and respiratory tracts, which verifies the previously reported predisposition to occur in these regions. This predisposition may be on an embryologic basis, because these organs develop from the primitive oropharyngeal cavity and its surrounding branchial structures where embryologic malformations frequently occur. Fifty-nine cases or over one-third of the reported cases were in the tongue. These lesions in the tongue are usually, although not always, benign.

DIAGNOSTIC CRITERIA

Gross Appearance: While there is no characteristic gross appearance of myoblastoma, and the diagnosis must be made on the microscopic findings, the tumor is usually discrete, rounded, or nodular. When in relation to a mucous membrane it tends to be polypoid, but lacks the lobulation and clubbed pedicles of a polypoid rhabdomyoma. Descriptive facts were mentioned in 29 cases and are quite varied.

The following excerpts from descriptions of tumors in various locations serve as examples of the varied gross picture presented:

Bronchus—pinkish gray; broad based and pedunculated
Orbit—walnut sized, attached to bone
Bladder—mushroom shape, irregular ulcerated surface
Bladder—pedunculated base; anterior wall covered with sessile papillomas
Spinal cord—cut like a fibroma
Thoracic wall—stony hard, encapsulated, firm, grayish with overlying skin red

TABLE I

REPORTED CASES OF MYOBLASTOMA

AUTHOR	AGE (YR.)	SEX	DURATION	LOCATION	SIZE AND SHAPE	MICROSCOPY	GROSS	TREATMENT	REMARKS
Muller[44]	--	--	--	Leg muscles at site of old ununited fracture	----	Typical, no striations	----	Amputation	Appearance and clinical behavior caused author to classify it as malignant myoblastoma
Cappell and Montgomery[10] Case 3	61	M	9 days	Bladder	2.5 × 2 cm. mushroom shaped	Neoplastic cells invading wall of bladder	Solid mushroom shaped; irregular, ulcerated surface	Excision, death on table	Died under anesthetic, no autopsy
Case 4	27	F	--	Bladder	Nutmeg	Typical	Pedunculated, base and ant. bladder wall covered with sessile papillomas	Excision and electrocoagulation	No recurrence 6 yr.
Case 5	52	M	3 yr.	Spermatic cord	6 × 4.5 cm. ovoid	Not typical due to curious hyaline stroma	Cut like a fibroma, in cord substance not attached to testicle	Excision	Injury (fall), "The patient made an uneventful recovery"
Case 6	60	M	2 yr.	Tongue (?) ranula	4 cm. in diameter	Malignant myoblastoma. No striations	1 cm. base, cleft near growth with ulceration in cleft	Diathermy, radium 14,620 mg. hr. in 6 mo.	Recurrent after excision; recurrence measured 1.5 × 1.0 × 1.3 cm., ovoid; radium had no effect on growth. Cervical glands enlarged but no biopsy, patient died sometime later—cause thought to be recurrence and sepsis

TABLE I—CONT'D

AUTHOR	AGE (YR.)	SEX	DURATION	LOCATION	SIZE AND SHAPE	MICROSCOPY	GROSS	TREATMENT	REMARKS
Morpurgo[43] Case 1	55	F	--	Tongue	Elevated 2 mm.	Typical	Spongy nodule, submucous tumor within muscle, yellowish brown	Excision	Mucosa normal
Case 2	65	F	--	Tongue	----	Much atypism, acceptable, malignant myoblastoma; longitudinal striations	Low, raised with central crater	Excision	
Case 3	65	M	--	Upper right leg	---- Nut sized	Myoblastoma, sarcomatoides	In the scar, white, encapsulated	5 radium applications, excisions	Multiple recurrence
Geschelin[21]	40	F	--	Left vocal cord	Pea sized	Abrikossoff type 4	----	Excision via endolaryngeal approach	No recurrence 18 mo. after last operation
Roffo[47] Case 1	--	--	--	Tongue	----	----	----	----	----
Case 2	31	F	3 yr.	Tongue (rt. dorsum)	Almond	Typical transitional phases seen; striations present	Hard, smooth, red surface	Excision	Hyperplasia of overlying epithelium, author feels it is degenerative and not a tumor
Glasunow[23]	32	M	4 mo.	Mid-tongue	1 cm. in diameter	Typical, no striations	----	Radium 7,200 and 9,600 mg. hr., partial excision plus 960 mg. hr.	Hyperplasia of overlying epithelium
Gander[20]	--	--	--	Tongue	----	----	----	----	----

Parreira and Nunes de Almeida[46] Case 1	--	--	--	Tongue	----	----	----	----	----
Case 2	--	--	--	Tongue	----	----	----	----	----
Geschickter[22] 3 Cases	44	F	--	Sacral subcutaneous	----	Typical	----	Excision, radiation	Groins dissected; recurrence in groins 5½ yr. after excision; radium implanted. Patient well 20 mo.
	--	--	--	Sacral subcutaneous	----	----	----	----	----
	--	--	--	Sacral subcutaneous	----	----	----	----	----
Geschickter[22] 1 Case	7	F	--	Skin of ear	6 × 4 × 3 cm.	Striations present	----	----	----
5 Cases	--	--	--	Muscles of extremities	----	----	----	----	----
2 Cases	--	--	--	Breast	----	----	----	----	----
1 Case	--	--	--	Tongue	----	----	----	----	----
1 Case	--	--	--	Vagina	----	----	----	----	----
1 Case	--	--	--	Oral cavity	----	----	----	----	----
Gray and Gruenfeld[24] Case 1	30	F	5 mo.	Anterior tongue	Hazelnut	Typical	Dome-shaped protrusion on dorsum, embedded in muscle, yellowish, firm and elastic	Excision	Intact overlying mucosa; no recurrence 4 yr.
Case 2	35	M	6 mo.	Left edge of tongue	6 mm. in diameter	Typical	Located submucosally	Excised with small margin	History of trauma (biting); intact grayish overlying mucosa; no recurrence 6 yr.

TABLE I—CONT'D

AUTHOR	AGE (YR.)	SEX	DURATION	LOCATION	SIZE AND SHAPE	MICROSCOPY	GROSS	TREATMENT	REMARKS
Case 3	55	F	--	Left chest below mammary fold	15 mm. in diameter	Typical; no transitions, no striations	Overlying skin red, encapsulated, firm, grayish	Excised	----
Case 4	30	F	1½ yr.	Tongue	Pea	Typical	Well demarcated, yellowish, no capsule		Tender, intact overlying mucosa, no recurrence 3 yr.
Case 5	--	F	--	Breast	10 cm. in diameter	Typical	Grayish, firm, encapsulated		
Bobbio[9]	33	M	--	Left vocal cord	----	Typical	----	Excision in pieces	Overlying epidermoid carcinoma of the mucous membrane
Lattes[37]	49	M	1 yr.	Tongue	Small circumscribed	Typical	----	Excision	
Eickhoff[18]	25	M	--	Tongue	Cherry	Has cross striation (?) atypical rhabdomyoma	Firm, irregular, grayish white	Excision	Epidermoid carcinoma of overlying mucous membrane
Grayzel and Friedman[25]	45	F	6 mo.	Thoracic wall	Globular 2.7 × 2.5 × 1.5 cm.	Typical, parallel rows of granules suggesting cross striations; transitional stages seen	Stony hard	Excision	No recurrence Dec., 1939, to April, 1941
Frenckner[19] Case 1	25	M	--	Introitus of larynx	Lobular 3.5 × 7.5 cm.	Not typical, all cells had both longitudinal and cross striations; resembles Abrikossoff's Case 6	Egg shaped and lobular but surface grayish red with hemp-seed-sized yellow spots	Excision, blunt dissection	No recurrence 2½ yr., tumor appeared to infiltrate clinically and microscopically at its base

Case 2	28	F	1 yr.	Trachea	Hazelnut 2.7 × 2 cm.	Typical, no striations; previously diagnosed as a rhabdomyoma	Encapsulated, broad base, sharply defined; cut surface grayish red	Transtracheal submucosal enucleation	No recurrence 3 yr.
Case 3	41	M	3 yr.	Lower lip	10 × 10 × 13 mm. in situ	Typical	Overlying mucosa bluish white, partly encapsulated	Excision	Palpable pea-sized submaxillary gland
Case 4	22	F	3-4 yr.	Tongue (rt. edge)	Pea sized	Typical	Considered to be a fibroma	Excision	Slight infiltration of tongue musculature
Case 5	48	M	1 mo.	Tip of tongue	Firm pea sized in center of a red spot	Typical	Hard and clearly defined	Excision	----
von Bahr[4]	49	F	years	Lacrimal sac	Large pea grossly, microscopically 4 mm.	Typical, longitudinal but no cross striations	Pea-sized tumor with superimposed inflammation and suppuration	Excision	----
Kramer[34]	15	F	14 wk.	Rt. lower lobe bronchus, posterior-mesial aspect	Completely occluded rt. lower lobe bronchus	Typical	Pinkish gray, broad based, pedunculated	Bronchoscopy and punch biopsy excision in 2 stages, diathermy coagulation	Symptom-free with neg. x-ray 5 mo. after first bronchoscopy; accompanied by lung suppuration and atelectasis
Leroux and Delarue[38] Case 1	37	M	--	Tongue	Small	Typical; apparent transition between granular and muscle cells	----	----	Overlying squamous epithelioma

TABLE I—CONT'D

AUTHOR	AGE (YR.)	SEX	DURATION	LOCATION	SIZE AND SHAPE	MICROSCOPY	GROSS	TREATMENT	REMARKS
Case 2	45	M	--	Tongue	Small	Typical; apparent transition between granular and muscle cells	----	----	Apparent transitions between granular and epithelioma cells even more convincing than between granular and muscle cells in both these tumors; overlying squamous epithelioma
Case 3	At birth		--	Upper gum	----	----	----	----	Thin overlying epithelium; apparent continuity between its cells and the granular cells
Sjogren[50]	8	M	5 mo.	Orbit	Walnut	Varied; myoblastoma with sarcomatous-like areas; in last recurrence longitudinal and cross striations	Walnut-sized nodular, adherent to periosteum, recurrent	Radium, later excision, recurrence; exenteration of orbit	Tumor enlarged; patient gradually failed and died, no post-mortem; cervical adenopathy, clinically not significant
Dustin[17]	30	M	--	Tongue	----	Typical; longitudinal and cross striations	----	----	----
Kernan and Crocovaner[29]	21	F	3 mo.	Left vocal cord	Posterior $\frac{2}{3}$ of cord	Typical	Friable	Excision	Hyperplastic overlying epithelium simulating squamous-cell epithelioma; one recurrence, no recurrence 8 mo. later

Imperatori[27]	23	M	10 mo.	Left vocal cord	Size of two peas, lobular sessile	Typical	Papillary, firm; pale yellow, homogeneous	Excision	Hyperplasia of overlying epithelium, mucous gland metaplasia columnar to squamous; no recurrence, 4 mo.
Martinez[41]	50	F	18 yr.	Tongue	Oval 2 × 1.5 cm.	Typical, longitudinal and cross striations	Raised with central white plaque	Excision	No recurrence 8 mo., hyperplasia of overlying epithelium
Cioni[11]	48	M	--	Left adrenal	Globular	Atypical	"Meaty" grayish white, mottled	--	Metastases to pleurae, patient expired
Tamis and Kowles[52]	39	F	3 yr.	Rt. labium majus	2.5 cm. in diameter	Typical	Firm and elastic, on cut section appears like dense connective tissue	Excision	No recurrence 1 yr.
Lino[39]	24	F	--	Tongue	----	Granular cells pleomorphic; many granular cells and some striations	----	Excision	----
Ducuing, Ducuing and Bassal[16] Case 1	34	M	20 mo.	Tongue	Small pea, round	Epidermoid carcinoma of mucosa; granular cell, myoblastoma below	Hard, yellowish	Excision	Patient well 4½ yr.
Case 2	52	M	2 mo.	Tongue	Small pea	Granular cell myoblast, epithelial hyperplasia	Whitish	Excision	Patient well 1 yr.
Case 3	22	M	2 mo.	Tongue	½ pea	Epithelioma granular cell	Hard	Excision and electrocoagulation	Patient well 1 yr.
Case 4	44	M	6 mo.	Tongue	Pea	Granular cell	Hard	Excision	Patient well 6 mo.

TABLE I—CONT'D

AUTHOR	AGE (YR.)	SEX	DURATION	LOCATION	SIZE AND SHAPE	MICROSCOPY	GROSS	TREATMENT	REMARKS
Seiffert[49]	47	F	--	Tongue	½ pea	Granular cell	----	Excision	Patient well 1 yr., marked epithelial hyperplasia
Civatte and Ducourtioux[12]	35	F	2 yr.	Tongue	2 × 1 cm.	Granular cell and some fibers with striations	Hard	Electro-coagulation	
Bang[5]	63	--	--	Tongue	----	Granular cell	Hard	----	Patient well 5 yr.
Bernier, Mann, and Ash[7] Case 1	2 wk.	F	--	Mandible and maxilla	----	Granular cell	----	----	----
Case 2	--	F	--	Tongue	----	Granular cell	----	Excision	----
Horn and Stout[26] Case 1	60	F	(?) 20 yr.	External auditory canal	Two pieces: 1.5 × 1.0 × 1.0 cm., 1.5 × 0.5 × 0.5 cm.	Typical	Grayish white with areas of hemorrhage	Excision	Lesion operated upon four times previous to last excision
Case 2	77	F	8 yr.	Rt. middle ear or external auditory canal	1.5 × 0.7 × 0.6 cm.	Typical	Bilobed, polypoid	Excision	----
Additional Cases 5	--	--	--	Tongue	----	----	----	----	----
1	--	--	--	Lip	----	----	----	----	----

2	--	--	--	Alveolar process of maxilla or mandible	----	----	----	----	----
1	--	--	--	Floor of mouth	----	----	----	----	----
1	--	--	--	Trachea and bronchi	----	----	----	----	----
3	--	--	--	Skin	----	----	----	----	----
10	--	--	--	Subcutis	----	----	----	----	----
1	--	--	--	Muscles of extremities	----	----	----	----	----
2	--	--	--	Breast	----	----	----	----	----
Thoma[53]	30	F	1½ yr.	Tongue (anterior third)	1.4 × 2.3 × 1.0 cm.	Typical	----	----	----
Syathmóry[51]	--	--	--	Vulva	----	----	----	----	Accepted in literature; original article not available to us
Kratochvil[35]	--	--	--	Alveolar ridge	----	----	----	----	Accepted in literature; original article not available to us
Loi[40]	--	--	--	Lower lip	----	----	----	----	Accepted in literature as a malignant tumor; original article not available to us
von Albertini[3]	--	--	--	Tongue	----	----	----	----	Original article not available to us

TABLE II

NEW CASES

OUR CASES	AGE	SEX	DURATION (MO.)	LOCATION	SIZE AND SHAPE	GROSS	ABRIKOSSOFF TYPE	TREATMENT	REMARKS
Case 1	35	F	2½	Left deltoid	4 cm. in diameter, fusiform	On section, firm, multicolored, retracted, poorly demarcated, infiltrating	Type 2	Excision	Later developed swelling over right humerus and over right ulna. These regressed on x-ray therapy. Patient had tetryl poisoning. Proved metastases to lungs, etc. Patient expired
Case 2	64	M	24	Left side of tip of tongue	7 mm. in diameter	Elevated 1 mm.; firm, whitish gray, granular	Type 2	Partial glossectomy	Mental case—no history; hyperkeratosis of overlying mucous membrane, no recurrence 16 mo.
Case 3	17	F		Left buttock	Size and shape of small hen's egg	Egg-sized mass; slightly movable	Type 2	Excision, x-radiation	Tumor occurred at site of trauma, no recurrence 1 yr.
Case 4	81	M	12+	Lower left thigh	2.5 cm. in diameter, ovoid	Adherent to fascia, ovoid, grayish white periphery, soft degenerated center	Type 2	Excision	One recurrence after primary excision; no recurrence one year after second excision
Case 5	24	M	24	Palm left hand	Pea size growing to olive size	First specimen not seen; second specimen indurated scar 7 × 6 × 3 cm.	Type 2	1. Excision 2. Partial amputation of hand 3. Amputation of forearm and axillary dissection	Large axillary lymph nodes, but all 52 nodes negative for tumor; no recurrence 6 mo. after excision

Case 6	52	F	1½	Midright thigh	10 cm. + in diameter	10 cm. in diameter; infiltrating 4 cm. in diameter fungating mass	Type 3	X-radiation	Local lesion disappeared after x-ray; died with pulmonary metastases
Case 7	71	M	1+	Buccal mucous membrane	4.5 × 3.5 × 2.5 cm.	Firm and gray, one necrotic surface	Type 3	Excision, x-radiation	Died with extensive cervical and pulmonary metastases
Case 8	66	M	1½+	Right pectoral region	20 × 16 × 6 cm., pedunculated	Whitish, dull tissue where not necrotic	Type 3	No treatment	Expired from sepsis secondary to the tumor
Case 9				Buttocks	9 cm. in diameter, spherical	Gray, well-demarcated but not encapsulated	Type 2	Excision	Specimen in Warren museum; no history available
Case 10	81	M		Left thigh			Type 3		Slide found in tumor clinic files; no history available

Larynx—egg shaped, lobular
Trachea—encapsulated with broad base
Vocal cord—friable, papillary, firm, pale yellow
Breast—grayish, firm, encapsulated

Myoblastoma of the tongue is usually found on the dorsum of the organ and is firm and discrete. These were firm or hard, whitish gray or yellowish on cut section. Some were well demarcated and others were not. Most were firm to hard, but one was spongy and soft. Two were raised, one with a central crater and another with a central white plaque. Thirteen of the tongue tumors in which the size was given were less than 1 cm. in diameter, and none exceeded 2 cm. in diameter.

The largest tumor so far reported (in the chest) measured 20 by 16 by 6 cm.; the smallest (in the tongue), 4 by 8 mm.

MICROSCOPIC CRITERIA

As may be gathered from Abrikossoff's[1, 2] classification, there is some variability in the appearance of the myoblastomas. Those with any

TABLE III

DURATION OF SYMPTOMS

PER CENT	BENIGN	PER CENT	MALIGNANT
31	up to 6 mo.	75	1 mo. to 6 mo.
17	6 mo. to 1 yr.	25	6 mo. to 2 yr.
14	1 yr. to 2 yr.		
38	2+ yr.		

TABLE IV

TOPOGRAPHY OF MYOBLASTOMA

LOCATION	CASES FROM LITERATURE	CASES FROM KLEMPERER	NEW CASES	TOTAL CASES
Tongue	37	21	1	59
Mouth	6	6	1	13
Skin	3	6		9
Larynx	5	4		9
Subcutaneous	10			10
Breast	5	2		7
Extremities	6	2		8
Leg	2	3	3	8
Lip	3	1		4
Chest	2		1	3
Ear	3			3
Sacral	3			3
Arm			2	2
Bladder	2			2
Buttock			2	2
Esophagus	1	1		2
Labium	2			2
Orbit	2			2
Trachea	2			2
Adrenal	1			1
Bronchus	1			1
Spermatic Cord	1			1
Spinal Muscles	1			1
Vagina	1			1
Total	99	46	10	155

appreciable number of cells containing cross striations we believe are better considered as rhabdomyomas or rhabdomyosarcomas rather than as myoblastomas. The myoblastoma may be made up of cells of very similar type or may be highly pleomorphic. If uniform in cell type the usual picture is that presented by the granular cell form. Here the cells appear almost epithelial in character. They are from 20 to 35 micra in diameter, polyhedral with fairly well-defined cell membrane and a finely granular cytoplasm. The ground substance of the cytoplasm does not take the stain at all well. The nuclei vary somewhat in size, are relatively small considering the size of the cell, and somewhat vesicular. Nucleoli are present but not especially prominent. Mitoses are absent or rare.

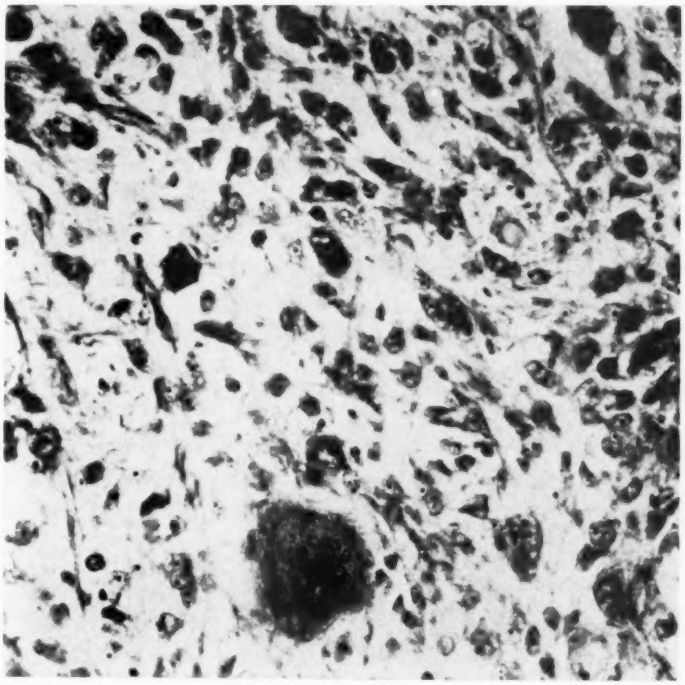

Fig. 7.—Myoblastoma, type 2 (Case 9). Note multinucleate cells. Phosphotungstic acid hematoxylin stain (×385).

These smaller cells may present a pseudo-alveolar arrangement or may lie in relatively large sheets. Scattered among them at times are elongated or even ribbonlike cells, usually with denser and more acidophilic cytoplasm and less granularity. These longer cells may be multinucleate. Grading from these to more unusual forms are varying sized masses of fairly acidophilic cytoplasm containing multiple nuclei which frequently are fairly uniform in size and resemble the nuclei of the granular cell type of myoblast. Sometimes, therefore, they may resemble foreign body giant cells. Occasionally the nuclei of these larger cytoplasmic masses may be markedly lobulated, very vesicular,

and sometimes contain vacuoles. In some of the larger cell masses, granulations are present in the cytoplasm. In a few of the cells, particularly in the better differentiated tumors, these may represent precursors of the cross striations. This type of myoblastoma rarely grades almost imperceptibly into the definitely rhabdomyomatous tumor, but usually is distinctive. The tumor is sometimes separated from adjacent normal muscle fibers by a definite connective tissue capsule. Often the peripheral cells interdigitate with the adjacent normal muscle bundles.

In the malignant variant of this tumor, the granular-cell type of myoblast may be in part replaced by more variable cells, among which a moderate degree of mitotic activity is present. The larger protoplasmic masses may contain very bizarre giant nuclei, sometimes showing evidence of abnormal mitoses and abnormal increase in chromosome number.

The stroma is usually fine and scattered. The degree of vascularization is variable, but blood channels are not a prominent feature of the tumor.

TREATMENT

On the basis of available data 37 patients were treated by surgical excision, 3 by excision and electrocoagulation, 5 by excision and radium therapy, and 1 by electrocoagulation. Follow-up data is too incomplete to be significant. It is presented in Tables I and II. A few points deserve emphasis. One patient had a recurrence and was well eight months after re-excision. Another had recurrence and metastases from the sacrum to the groin five and one-half years after primary excision and was well twenty months after dissection and radium therapy. One patient remained well five months after bronchoscopic electrocoagulation.[34]

One patient with tumor of the leg had five applications of radium, dosage not specified, and excision for recurrences; the end result is unknown.[43] One myoblastoma of the tongue was treated by electroexcision followed by 14,620 mg. hr. over a period of six months. The patient later died.[10] One myoblastoma of the orbit was treated by extensive radium therapy, dosage unknown, followed by excision and later exenteration of the orbit. The patient finally died of the disease.[50]

We know of only 5 patients treated with radium. In one tumor of the tongue there was relief of pain but no effect on the growth. In the previously mentioned myoblastoma of the orbit, and in one of the leg, radiation had no apparent effect. In our Case 3, L. F., from the Westfield State Sanatorium, x-radiation was applied to the tumor bed after the tumor had been excised. In Case 6, the patient responded to roentgen therapy. The local tumor regressed completely, but the patient died of pulmonary metastases.

MALIGNANCY

In searching the literature on myoblastoma for cases with evidence of malignancy, two facts are outstanding:

1. Locally invasive and histologically malignant tumors exist, although they are rare.
2. Metastasis either by blood stream or lymphatic channels is unusual.

Some myoblastomas were coincident with carcinoma. These usually developed in the upper respiratory passages and skin as a result of the abnormal proliferation of the overlying epithelium, which characterizes many myoblastomas. Data as to this feature are available in 29 cases and, of these, in 13 or 45 per cent there was abnormal proliferation and in 8 or 28 per cent there was definite epidermoid carcinoma. In the remaining 8 cases, the condition of the overlying epithelium was normal.

Leroux and Delarue,[38] in reporting two tumors of the tongue, thought that the apparent transitions between granular cells and epithelioma cells were even more convincing than between granular and muscle cells, but this is not the prevalent opinion.

In 10 of the cases from the literature and 4 of our own, there was either gross or microscopic evidence of local invasion or malignancy of the myoblastoma itself. Although there was regional adenopathy in 7 cases, in only 3 (Geschickter's and our Cases 1 and 7) were metastases to lymph nodes proved by biopsy.

The following are brief abstracts of those reported cases we consider as showing malignant characteristics:

Myenburg[45] reports a case of myoblastic sarcoma of the tongue in a 57-year-old man which presumably recurred after excision, was locally malignant, and resulted in hemorrhage and death.

The tumors in two of Morpurgo's[43] cases showed malignant characteristics, and study of his photomicrographs gives convincing evidence. The first was a tumor of the dorsum of the tongue in a 65-year-old woman and was diagnosed clinically as a carcinoma. It was described as a villous excrescence, later progressing to a raised lesion with a central undermining crater. Dental trauma was thought to be a factor. No metastatic nodes were demonstrated. The tumor was excised and the specimen consisted of nearly all of the left dorsum of the tongue. There were many mitotic figures and the tumor was invasive. No follow-up is given.

Morpurgo's second case was that of a 65-year-old man who had a nodule excised from the upper portion of the right leg following five applications of radium. The tumor recurred twice after excision. A microscopic diagnosis of myoblastoma sarcomatoides was made on the basis of its being more primitive and complex, simulating spindle-cell sarcoma. This case would apparently fall under type 3 in Abrikos-

soff's[1] classification. There appears to be no necessity for the term myoblastoma sarcomatoides.

Cappell and Montgomery[10] quote briefly a case recorded by Muller,[44] in 1917, as a rhabdomyoma, which they feel should be classified as a malignant myoblastoma. This was a tumor originating in the skeletal muscles of the leg at the site of an ununited fracture. The tumor failed to exhibit striations, but its staining and morphology indicated its origin from striated muscle. The subsequent history after amputation is not recorded but the appearances and clinical behavior suggest that the growth was malignant.

The same authors[10] present two of their own cases. The first was a myoblastoma of the tongue in a 60-year-old man, diagnosed clinically as a ranula and excised. It recurred a year later together with cervical adenopathy. It was excised and recurred again two years later and grew to involve the right tonsil and anterior pillar. It was treated by diathermy and radium to the extent of 14,620 mg. hr. The radium diminished the pain but had no effect on the growth. The patient eventually died and, although there was no autopsy, it was thought that death was due to recurrence in the mouth and nodes followed by sepsis. The photomicrographs are acceptable as myoblastoma. Metastasis was not proved pathologically.

Their second malignant case was a myoblastoma in the bladder of a 61-year-old man, with hematuria for nine days. Cystoscopic examination and later cystotomy revealed a mushroom-shaped stalk 2 cm. long and 2.5 cm. in diameter, about one and one-half to two inches above the ureteric ridge. Unfortunately, the patient died under anesthesia. Microscopic examination of the removed specimen showed invasion of the bladder wall, so that, had the patient lived, there would have been a recurrence. The cytology in the accompanying photomicrographs is consistent with the diagnosis of myoblastoma.

Sjogren[50] reports a case of malignant myoblastoma of the orbit in an 8-year-old boy. A tumor was excised from under the left orbital ridge and at first was diagnosed as xanthosarcoma. It recurred postoperatively, and he developed cervical adenopathy, which was thought not to be significant. A course of x-ray therapy had no effect and the tumor was again excised and found to involve the superior oblique muscle and supraorbital nerve. It again recurred and finally an exenteration of the orbit was done, but there was further recurrence involving the bony structures of the orbit, and the patient finally died with a large protruding, painful, fluctuant tumor. The microscopic pictures of the later recurrence were compatible with myoblastoma. In certain fields there was a sarcomatous appearance and there were a few striated cells present.

Geschickter[22] reports a case of proved metastatic myoblastoma in a woman aged 44 years, with metastases to both groins from the region of the sacrum. Five and one-half years after excision of the primary

lesion there was an ulcer at the site of the original growth and masses in both groins, larger on the left. The growth on the right was excised and found to be well encapsulated. On the left, the growth infiltrated the surrounding tissue and was adherent to the femoral artery. Some tumor tissue was left behind on the artery and four 1 mc. radon seeds were implanted. The patient was reported well twenty months later. Through the courtesy of Geschickter and Horsley, we have been able to examine the slides of the lesion, which appear typical.

Cioni[11] reports a case of a malignant myoblastoma of the adrenal gland with metastases to the pleura in a 48-year-old man, which appears acceptable as an Abrikossoff type 4 tumor.

Loi[40] reports a case of a malignant myoblastoma of the lower lip. The description is not available to us, but other writers have recorded it as malignant.

Our own cases of malignant myoblastoma are reported as Cases 1, 6, 7, 8, and 10. That the more histologically variable types of myoblastoma may metastasize has been clearly proved. The commoner sites for these metastases are the regional lymph nodes and the lungs.

In most of the malignant cases, it was noted that there was: (1) atypism of cells, (2) excessive mitotic figures, (3) spindle-shaped cells, and (4) local invasion.

Age had no clear influence on the occurrence of malignant myoblastic tumors. The patients ranged from 8 to 81 years of age, although 9 of 13 were over 50 years of age.

CONCLUSIONS

1. Myoblastoma is a tumor entity becoming more generally recognized. It is derived from embryonic myoblasts and may be distinguished from the rhabdomyoma group.

2. We have reviewed the clinical data and microscopic findings of 104 cases collected from the literature, exclusive of those reported by Klemperer, and present 10 new cases.

3. Fifty-six per cent of these occur in the upper respiratory and digestive tracts.

4. Fifty-nine cases occurred in the tongue and of these, 3 or 5 per cent were malignant.

5. Eleven per cent of the total cases were malignant and of these, only 3 showed proved metastasis.

6. Whenever a myoblastoma is reported to have (1) atypism of cells, (2) excess mitotic figures, (3) spindle-cell or sarcomatous pattern, or (4) local invasion, it should be treated surgically as a malignant tumor until more is known of the nature of these growths, especially if the patient is over 50 years of age.

7. The degree of radiosensitivity and frequency of metastasis are as yet unknown. Both appear to be low.

8. Tumors under mucous membrane or skin have a marked tendency to be associated with hyperplasia and epidermoid carcinoma of the overlying epithelium.

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MALIGNANT PAPILLARY CYSTADENOMA OF SWEAT GLANDS WITH METASTASES TO THE REGIONAL LYMPH NODES

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ALTHOUGH sweat gland tumors have been recorded in the literature not infrequently, reports of cases of proved malignancy are rare. Most of the carcinomas of sweat glands which have been described were considered malignant on the basis of histologic invasive or anaplastic growth, metastasis being exceptional. In this communication, a sweat gland tumor of well-defined papillary structure is described which, in addition to showing invasive growth locally, metastasized to the regional lymph nodes.

Gates, Warren, and Warvi[1] have recently published a review of tumors of sweat glands. They collected from the literature twenty-nine cases of carcinoma which they considered to be clearly of sweat gland origin and added six of their own. Among the tumors of questionable malignancy which they excluded are the numerous reported cases of adenocarcinoma of the vulva (McDonald[2]), which, with the exception of Eichenberg's[3] tumor, have not metastasized. Metastasis occurred in only four of the thirty-five cases reviewed by Gates and associates. Hedinger[4] reported a sweat gland carcinoma of the scalp, which was excised together with two 1 cm. cervical lymph nodes which were the site of metastases. The tumor reported by Hufschmitt and Diss[5] also involved the scalp; six months after excision, it recurred with regional metastases. It was adherent to the periosteum of the skull. Moriconi[6] described a sweat gland cancer which arose in the axilla and metastasized to the axillary nodes. The patient was well and without evidence of disease five years after excision of the primary tumor and radical axillary dissection. Eichenberg[3] described a tumor occurring on the labium majus and giving rise to one small inguinal lymph node metastasis. An additional case is that recorded by Suzuki[7] of a medullary sweat gland carcinoma of the patellar region, which metastasized to the inguinal and femoral lymph nodes.

In addition to these cases with metastases, four of the tumors reported by Gates and co-workers and two of the tumors collected by them from the literature (Morisani,[8] Diss and Peterschmidt[10]) recurred locally fol-

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lowing surgical excision. Morisani's tumor also invaded the tarsal bones, and that described by Thierfelder[11] invaded the frontal bone and the meninges. One of Gates' tumors invaded the auricular cartilage.

CASE REPORT*

L. K. (No. 50925), a 31-year-old Hebrew man, was first admitted to the Hospital of the University of Pennsylvania, May 13, 1942, with a painless, slowly growing mass on the radial aspect of the left wrist, about 4 cm. proximal to the radial styloid. It had first been noted fifteen years before (1927), several months after an accident in which a steel sled runner had passed over the wrist without, however, producing serious injury (Fig. 1). The lesion was biopsied in 1931 and again in 1933. At this time the patient first complained of diminution in sensation over the dorsal and radial portion of the left hand. No treatment was attempted

Fig. 1.—Reproduction of a snapshot of the patient at the age of 16. The tumor of the left wrist is readily visible.

until 1937, when the lesion was excised. The tumor began to recur nine months after this procedure and a second excision was done in 1940. Shortly after this, enlargement of left axillary and epitrochlear lymph nodes was noted. Another biopsy was done in May, 1941, after the tumor had again recurred locally. These surgical procedures were carried out by different surgeons in different hospitals.

The physical findings on admission to this hospital were limited to the mass on the radial side of the left forearm just proximal to the wrist, which measured 10 by 5 by 2 cm., and discrete, enlarged nodes in the left axillary and epitrochlear regions. Sensation was diminished over the dorsal and radial part of the hand

*This case is reported with the permission of Dr. William H. Erb.

and the left radial pulse was weak compared with the ulnar. X-rays of the left wrist showed a large defect in the distal portion of the volar aspect of the radius associated with a soft tissue mass (Fig. 2).

May 15, 1942, a left axillary dissection was carried out and two weeks later, several days before discharge, the lesion of the forearm was biopsied. The patient was readmitted June 21, 1942, and excision of the primary tumor was attempted the following day. An incision was made on the radial side of the forearm. Widespread invasion of the soft tissues, including the muscles, and of the radius

Fig. 2.—X-ray of forearm, showing destructive lesion of the distal part of the radius.

was found. Although much of the tumor was removed and the cavity in the radius was curetted, all of the tumor could not be reached through this incision and the operation was terminated. Another attempt was made to excise the local tumor, this time through an incision on the flexor surface of the forearm, July 6, 1942, but the disease was too extensive to permit complete removal. June 29, 1942, an enlarged epitrochlear lymph node was removed.*

*This specimen was examined by Dr. William E. Ehrich, Chief of the Division of Pathology of the Philadelphia General Hospital, who has kindly permitted me to study the sections. The patient was discharged July 15, 1942.

Between July 22 and Aug. 21, 1942, the axilla was treated with x-ray irradiation. A total of 5950r was delivered through 15 by 20 cm. anterior and posterior fields and a direct axillary field 9 cm. in diameter. The factors were 200 kv., 15 Ma., 50 cm. skin-target distance and filters, 1 mm. Al and ½ mm. Cu. (200r had previously been given to the epitrochlear region).

The patient was admitted for the third time Oct. 30, 1942, for excision of two recurrent nodules in the forearm, and for the fourth time Jan. 7, 1943, for repair of an indirect inguinal hernia. X-rays taken Oct. 31, 1942, showed considerable filling in of the defect in the radius.

When the extent of this patient's disease was first realized, amputation of the arm was advised. He repeatedly refused to consider radical treatment until December, 1943, by which time the arm and hand were markedly edematous and there were extensive recurrences palpable in the scarred area on the radial aspect of the forearm (Fig. 3). On December 13, 1943, amputation was performed just distal to the deltoid insertion but above the upper limits of the edema.

Fig. 3.—Photograph of the patient one month before amputation. In addition to the tumor and scarring of the forearm, there is generalized swelling below the midportion of the arm.

PATHOLOGIC DESCRIPTION

Gross.—The arm, amputated 12 cm. above the elbow, was greatly swollen, large amounts of thin clear fluid escaping from the tissues on incision. A large tumor mass invaded and destroyed all the soft tissues of the dorsal part of the distal 12 cm. of the forearm, involving to a limited degree the radial aspect of the palmar surface as well. The skin overlying this mass was extensively scarred and firmly bound to the tumor tissue. The distal 4 cm. of the radius was destroyed

by the tumor, only segments of the cortical outline being discernible (Fig. 4). Proximal to the area of destruction, the bone was rough and extremely dense with a very small marrow cavity. Although surrounded on three sides by the growth, the ulna was not involved. The radiocarpal joint was invaded at one point, there being a small area of neoplastic involvement of the lunate bone and the articular cartilage.

The tumor was composed of adherent nodules varying in diameter from a few millimeters to 1.5 cm. Some of these, in general the smaller ones, were solid but soft, pale gray, and frequently gelatinous. Other nodules were larger and dark blue, proving to be thin-walled cysts containing moderately thin, bluish-red fluid. Soft, pink tissue was usually found adherent to the lining of these cysts, at times completely filling them.

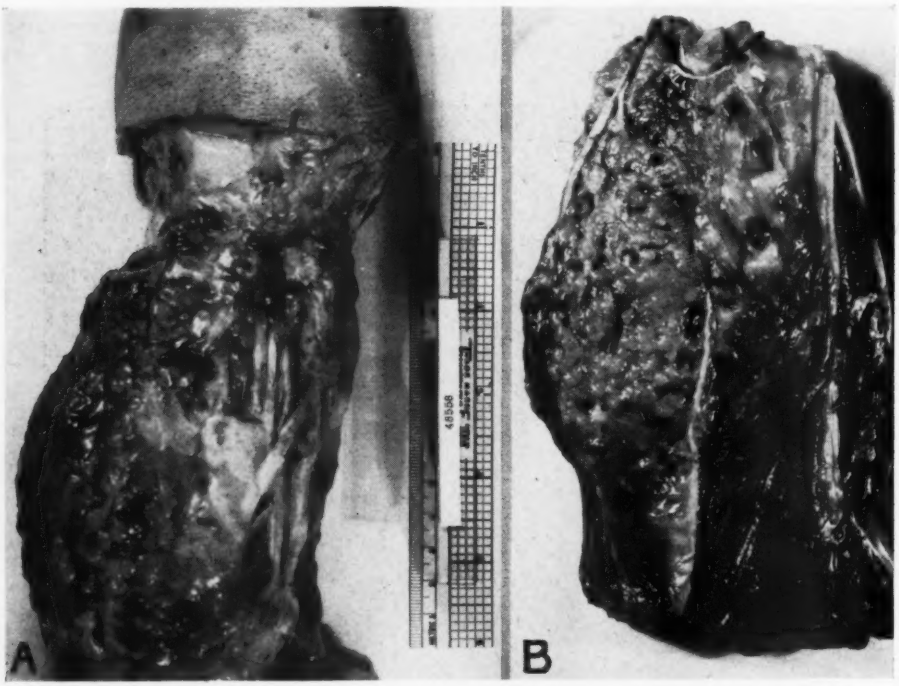

Fig. 4.—Gross appearance of the tumor. *A* shows the dorsal aspect of the forearm, *B* the cut surface. The arrow indicates the radiocarpal joint, adjacent to which a small portion of the radius is preserved.

A mass of similar tumor tissue about 3 cm. in diameter was also found in the depth of the operative scar in the epitrochlear region.

The tumor had a similar gross appearance in all of the specimens previously excised and studied in this laboratory, including the axillary lymph nodes.

Microscopic.—The tumor was composed of a number of cystic cavities sometimes lined by a single layer of epithelium, but more often with a papillary growth which more or less filled the lumen. The cells were generally cylindrical or cuboidal. The nuclei were ovoid and fairly uniform. Some of the cells contained droplets of material which had the staining properties of mucin. This material was abundant in the gland spaces formed in many of the more solid papillomas (Fig. 5). Fresh hemorrhage and deposits of hemosiderin were observed in the lumens and walls of many of the cysts. In general the cysts were well circumscribed, the tumor tissue being confined within them. These cysts were widely distributed throughout the soft tissues, invading especially the skeletal muscles (Fig. 6). The

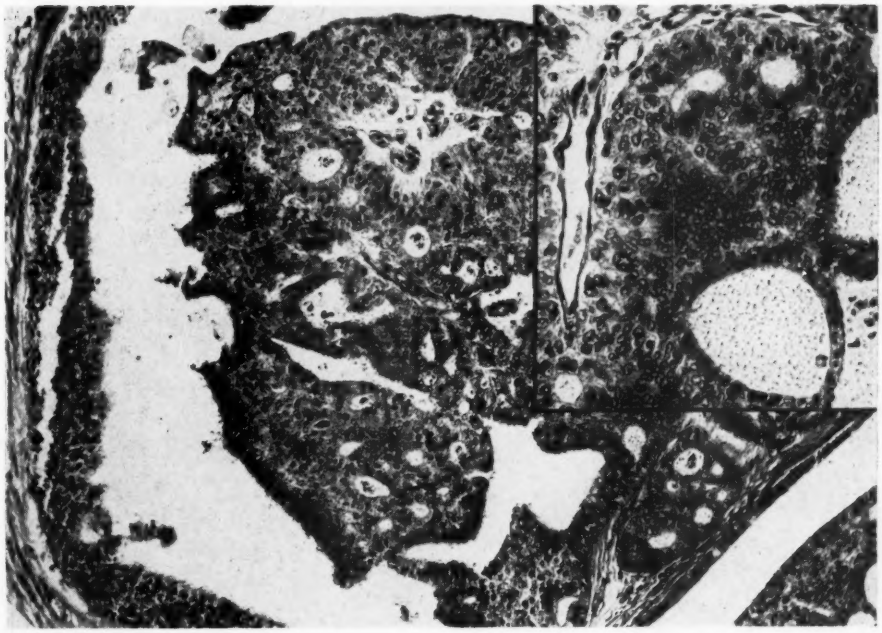

Fig. 5.—Photomicrograph illustrating the intracystic papillary structure of the tumor (hematoxylin and eosin, ×150). The inset shows the glandular pattern in a higher magnification (hematoxylin and eosin, ×300).

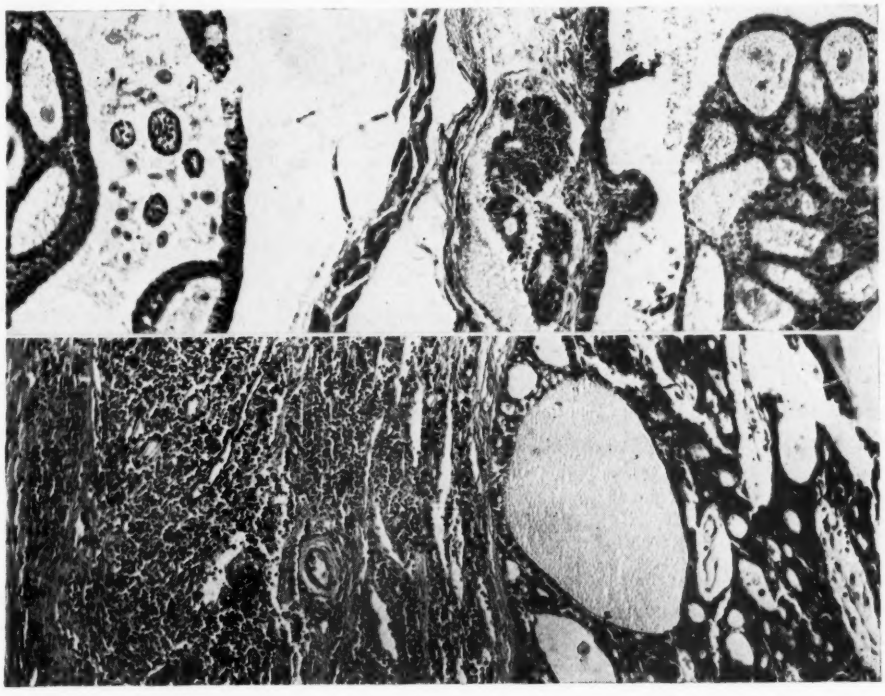

Fig. 6.—Malignant papillary cystadenoma of sweat glands invading skeletal muscle (hematoxylin and eosin, ×150).

Fig. 7.—Epitrochlear lymph node metastasis (hematoxylin and eosin, ×150).

histologic appearance of the tumor was essentially the same in all the sections from all of the specimens studied, with the single exception of the radius. The metastases in the lymph nodes also showed this structure (Fig. 7). In the radius, cyst formation was noted only occasionally and the tumor freely infiltrated the marrow spaces. Fibrous stroma was abundant only in some of the latter areas (Fig. 8).

The tumor did not show the anaplastic qualities usually associated with malignancy and mitotic figures were rare. New bone formation was observed beneath the periosteum of both the radius and ulna but the tumor did not invade the latter.

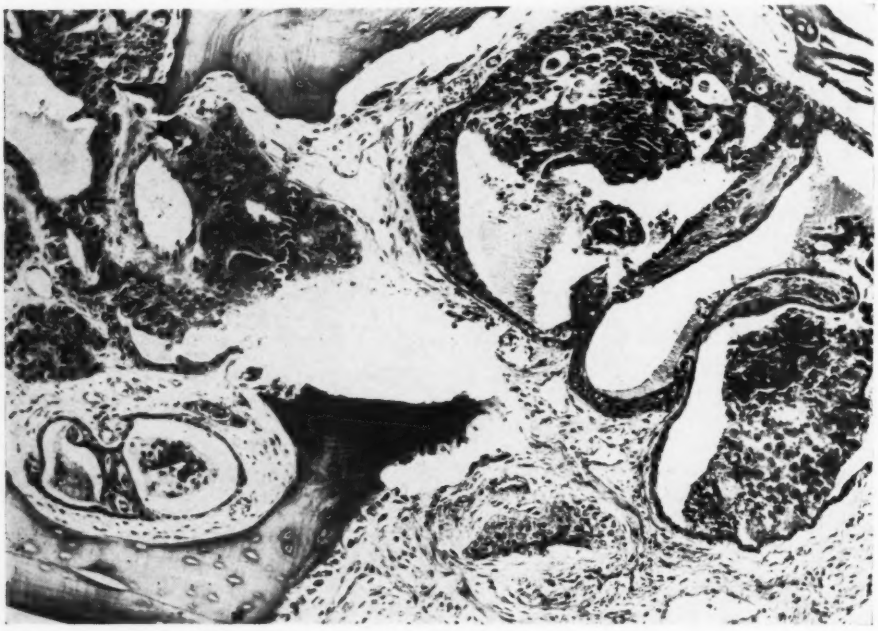

Fig. 8.—Photomicrograph showing invasion of the distal part of the radius (hematoxylin and eosin, ×150).

COMMENT

This tumor corresponded morphologically with the group of sweat gland neoplasms classified as hydradenoma papilliferum by Gates, Warren, and Warvi, and resembled the lesions reported in the literature as syringadenoma papilliferum or nevus syringadenomatosus papilliferus (Werther[12]) or as hidradenoma (Pick[13]). Not only the local lesions in this case, but even the lymph node metastases had a striking, intracystic papillary structure. Only where it invaded the radius did the tumor tend to lose this appearance and to infiltrate the tissues diffusely.

Gates and associates regard three of their hydradenoid carcinomas as having arisen from pre-existing tumors of the hydradenoma papilliferum type, but they did not maintain a papillary structure throughout. The metastasizing tumor of the vulva reported by Eichenberg appeared to have a similar origin and Hedinger's tumor had a gross papillary configuration, and histologically some portions showed the formation of papillae. The seventeen-year history in the case under discussion

indicates a relatively low grade of malignancy and suggests that this malignant tumor may have arisen from a cystadenoma.

In addition, this tumor resembled the reported sweat gland carcinomas of proved malignancy in that metastasis was limited to the regional lymph nodes. Similarly, bone invasion has been previously recorded (Morisani[8] and Thierfelder[11]).

The principal consideration in differential diagnosis was metastatic carcinoma, in particular metastasis from a papillary carcinoma of the thyroid gland. However, this appeared to be very unlikely in the light of the clinical course and in view of the abundant mucicarminophilic material present in the tumor.

SUMMARY

A malignant sweat gland tumor has been described which arose in the forearm of a 33-year-old Hebrew man. It was first noted when the patient was 16 years old. Over the course of 17 years, it recurred locally four times, invaded the radius, and metastasized to the epitrochlear and axillary lymph nodes. In all of its manifestations, the tumor showed an intracystic papillary structure. At the time of this communication, twenty-two months after pathologic demonstration of bone invasion and extension to the regional lymph nodes, and three months after amputation of the arm, there is no clinical evidence of distant metastasis.

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EXPERIMENTAL OBSERVATIONS ON THE HUMAN ILEOCECAL VALVE*

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THE reports of Macewen,[1] Rutherford,[2] Short,[3] Bargen, Wesson, and Jackman[4] indicate that the opportunity for prolonged and repeated observations on the ileocecal valve usually do not materialize. White, Rainey, Monoghan, and Harris[5] reported at length upon the nervous control of the sphincter and its reaction to certain drugs. As a result of the thoughtful awareness of Dr. Clarence Dennis concerning my interest in this junction of the alimentary tract, the following observations were made possible on the ileocecal junction of a patient for whom Dennis had necessarily exteriorized a portion of the lower ileum and cecum.

CONDITIONS OF THE EXPERIMENT

The patient was a 26-year-old French-Indian woman in an excellent state of nutrition. The observations were made two months after the exteriorization procedure, during a period of four weeks prior to a right hemicolectomy. The patient was on a general hospital diet and weighed 121 pounds. No medication was given other than that required for these experiments. Observations were usually continuous from 8:00 A.M. for a period of ten to twelve hours, with occasional rest periods.

The cecum was open, and attached to the abdominal wall in such a fashion as not to permit encroachment of the parietes upon the terminal ileum or the ileocecal valve. Approximately 10 cm. from the valve the lower ileum were exteriorized and completely cut across so that all intestinal content was evacuated through a proximal external ileal fistula. No intestinal content was transported by way of the distal ileal loop into the cecum. In the immediate area of the proximal fistula were numerous loops of small intestine with fistulous openings from which intestinal content escaped.

THE ILEOCECAL EMINENCE

The lips of the valve were thin, 2 to 5 mm. thick, depending upon the state of contraction. The superior lip projected from the cecal wall 3.5 cm. and the inferior lip 2.5 cm. The aperture varied in size and shape, depending upon the state of activity. At rest it was a narrow transverse, oval orifice 3.0 cm. long, with the frenulum distinctly visible. When contracted it appeared erectile, broader at its attachment to the

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cecal wall, and gently tapering to a rounded extremity 2.0 cm. across with the orifice closed and bounded by an everted border of puckered mucosal folds.

The ileocecal prominence was normally a deep pink in color, and generally in a semirelaxed state whether the patient were awake or asleep, except immediately before and during eating, when propulsive and segmental activity became evident by contraction of the entire structure and lengthening and shortening as it appeared to project and retract. At times a gelatinous mucous secretion would be actively extruded through the lips.

Palpation of the contracted structure revealed that the apex consisted of soft yielding tissue (the arches* of the frenulum) which would admit the tip of the finger with slight resistance. Within the lumen, and for approximately 1.0 cm., an increase in resistance was noted which could be overcome by gentle pressure. Just beyond this area, for a depth of 2.0 cm., a region of contraction was encountered beyond which the finger could not be passed until relaxation occurred. Persistent effort to do so caused the patient pain, which was referred to the epigastrium, and damage to the mucosa as evidenced by tears in the ileal mucosa and slight hemorrhage. When relaxed, the limits of these areas could not be recognized.

TYPE OF ILEOCECAL VALVE

The medial and lateral frenula of the valve were plainly visible, except when the ileocecal structure was completely relaxed. The medial frenulum was formed by the medial superior and medial inferior arches[6] of the valve. The lateral frenulum appeared to have divided into separate lateral inferior and lateral superior arches (Fig. 1), however after examination in the fresh state and later after fixation, the lateral superior and inferior arches were observed to form the lateral frenulum (type I ileocecal valve).

APPARATUS

Satisfactory kymograph records were obtained with Elliott's[7] balloon applicator connected to a spirometer type volume recorder with a writing lever. Tandem balloon records were obtained by an independent balloon-tambour system[8] attached to the Elliott applicator, so that both balloons were spaced independent of each other and used as a single instrument. The Elliott system, when filled with 7.0 c.c. of air, exerted a pressure sufficient to sustain an 8.0 to 10.0 cm. column of water.

SPONTANEOUS ACTIVITY OF THE TERMINAL ILEUM

Qualitative and quantitative control studies of spontaneous activity of the extramural terminal ileum, the sphincter, and ileocecal valve were

*The word arches, as applied here and in a previous publication[6] was suggested by Edward A. Boyden, Professor of Anatomy, University of Minnesota Medical School.

recorded during twenty periods of 30 to 120 minutes. Additional control records were obtained between the drug experiments.

Control records revealed that there were periods of quiescence and activity in all three areas. The activity of the segments varied, but at times all the segments were quiet. During periods of motility the proximal exteriorized small bowel loops were equally and similarly active, expelling intestinal content. At no time was spontaneous activity in the ileocecal lips, sphincter, or extramural terminal ileum noted independent of activity in the proximal ileal loops.

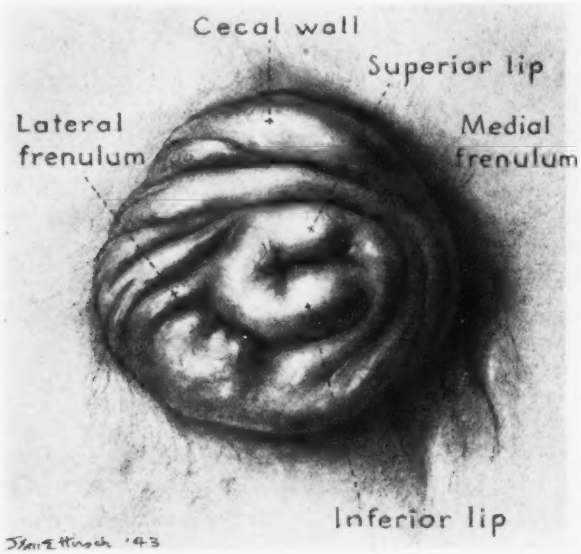

Fig. 1.—Artist's sketch of the ileocecal valve and the cecum.

The extent and frequency of contractions varied, being most energetic in the morning and less active in the evening. Propulsive activity constituted a small fraction (10 per cent) of the total motility which was nonpropulsive, with varying states of tone. At times activity of the sphincter consisted of continuous contractions and relaxations over a period of an hour, then the interval between contractions would lengthen until twenty to thirty minutes would expire. During such times a semirelaxed state would be effected. During evacuation at the proximal fistula (usually two to three hours after a meal) a short comparable period of sphincter and valve motility occurred followed by relaxation of the entire intracecal portion of the terminal ileum.

EFFECT OF MECHANICAL STIMULATION

The valve or sphincter was not observed to maintain a state of prolonged steady contraction, or spastic tonus. Several hundred contractions were recorded from different areas of the intramural and intracecal terminal ileum. The range of duration of contraction was

ten seconds to three minutes. The greatest reaction to any stimulus resulted when a stream of water or a foreign body was introduced into the orifice of the valve.

Introduction of the finger into the relaxed structure produced a contraction along the entire extent of the intracecal portion of the terminal ileum, which grasped the finger at once and held it steadily.

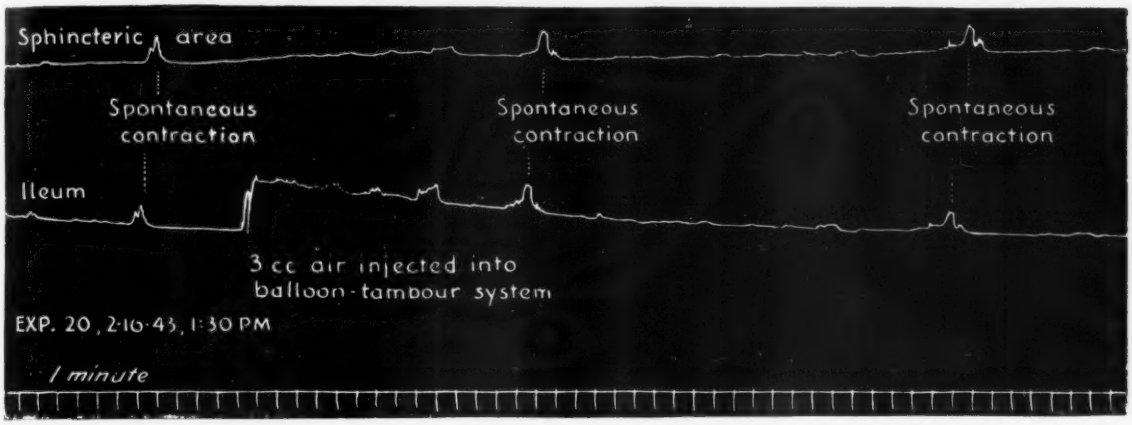

Fig. 2.—Tandem balloon kymograph tracing of the spontaneous activity of the ileum and ileocecal sphincter. There are independent spontaneous contractions in both areas. Air was injected into the ileal balloon system to test the independence of the two systems. Identical types of waves occurred in the ileum and sphincter area, reproduced by different recording systems.

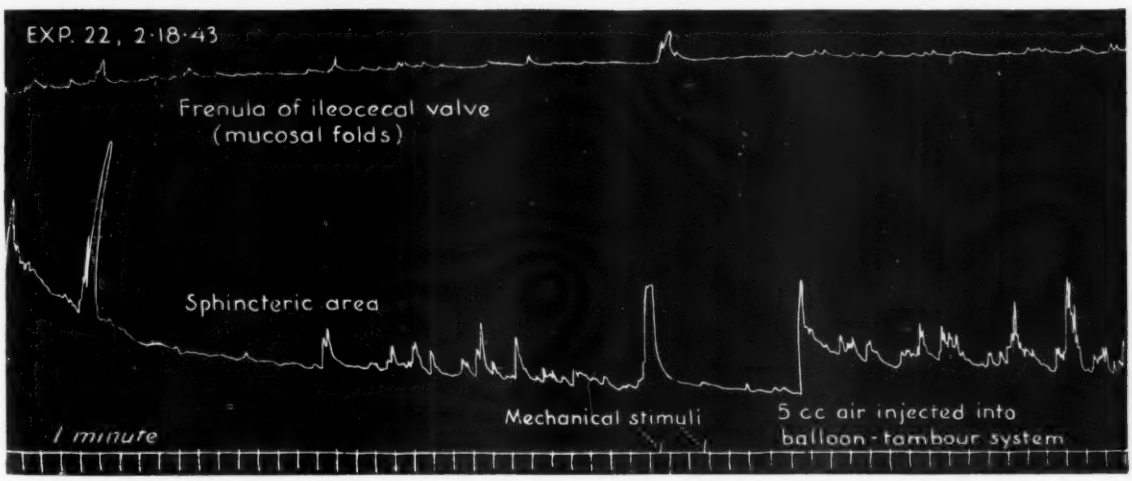

Fig. 3.—Kymograph tracing of the activity of the ileocecal valve and the ileocecal sphincter. Spontaneous independent contractions and contractions resulting from mechanical stimulation occur simultaneously in both structures. The injection of 5 c.c. of air into the balloon-tambour system illustrates the independence of the two balloons residing within the sphincter and within the lips of the ileocecal valve.

Ileal waves could be felt blending into or dying out as they reached an area of increased contraction at the intramural portion of the terminal ileum. Momentarily the grip was firm, then longitudinally and circumferentially segmental areas would slightly relax and con-

tract. Shortly, a definite propulsive wave from the ileum would pass through the entire structure, terminating by contraction of the valvular lips. A pause of relaxation ensued, then the cycle would repeat with somewhat less intensity.

A gentle brush of the mucosa of the cecum or either frenulum would produce a contraction of the valve, and sphincter, after two to three minutes relaxation would be complete except for numerous segmental movements of the valvular lips. A strong stimulus would produce in the patient a vague epigastric distress, which at times amounted to pain. This subjective complaint preceded the actual contraction by three to five seconds. During such a contraction the orifice would be tightly closed, preventing the introduction of an instrument without damaging force.

Twelve periods of thirty to ninety minutes were utilized to record the results of mechanical stimulation. The application of any adequate stimulus, such as stretching by the introduction of an instrument into the sphincter area, was followed by a latent period of two to twenty seconds before contraction started. A summation of stimuli could be produced at the time of the original stimulus and in the early phase of contraction. During the phase of relaxation the structure was not constantly refractory, as contractions could be produced, but these were not as strong as the initial responses. During the recovery period no prediction of its duration could be made, as often considerable time would elapse during which the structure was refractory to all forms of stimuli. The irritability of the area was generally the same for the period observed, although fatigue or adaptibility was observed to occur after a particularly active sequence of events. The best results were obtained when the patient was enthusiastic about the work to be done. Bad news or disagreeable circumstances noticeably inhibited the activity of the small intestine, sphincter, and valve. Occasionally experiments were suspended or postponed due to marked reduction in irritability.

ELECTRICAL STIMULATION

Stimulation with a constant break and rapid tetanizing current of a Harvard inductorium, using the device of Boyden[9] which consisted of a standard Rehfuss tube transformed into an electrode by inserting a copper wire through the oral end of the rubber tubing and connected to the primary of the inductorium, and the secondary coil connected to a moist lead electrode on the patient's arm, failed to produce a contraction when applied to the mucosa of the cecum, of the intramural terminal ileum, of the sphincter area, or the ileocecal valve (Fig. 4). Induced current stimuli were accompanied by contraction of the ileum when the electrode was placed proximal to the intramural portion of the terminal ileum. Inconclusive results attended a second experiment using fine silver wire clips as the primary electrode.

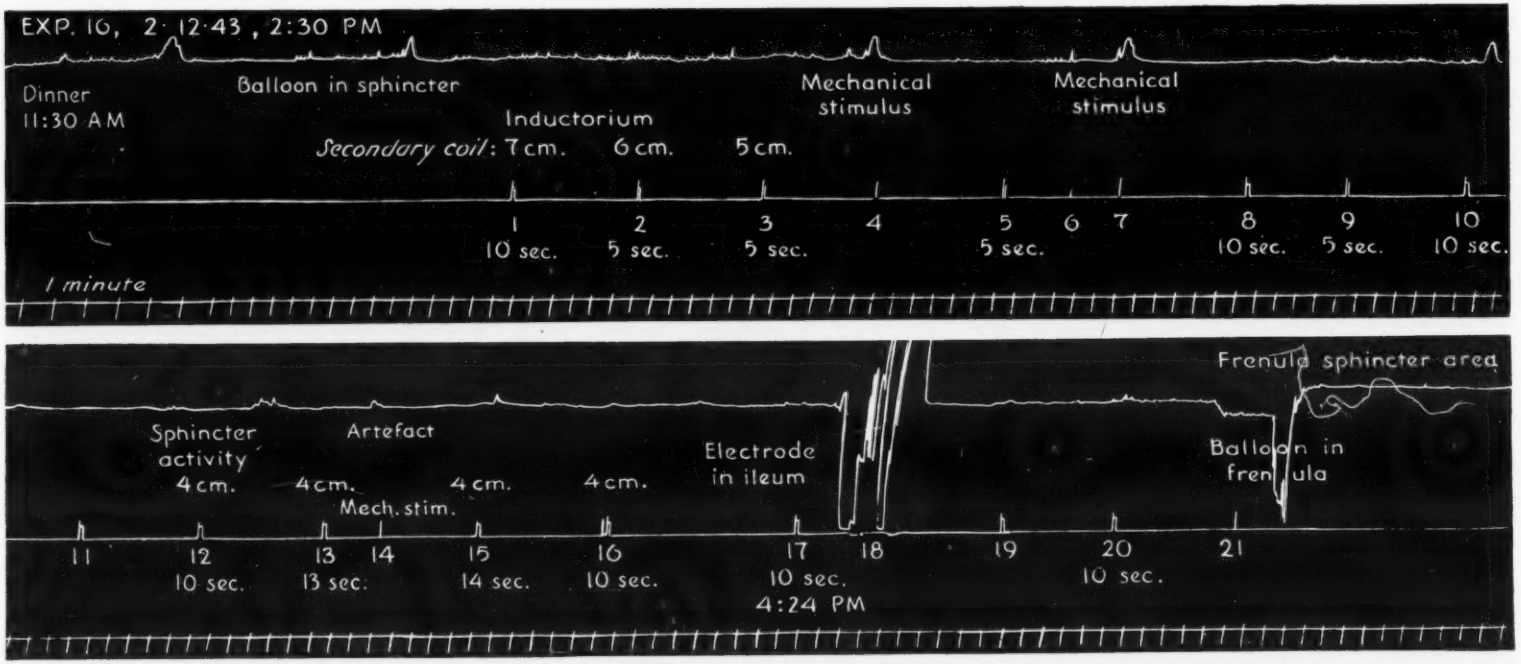

Fig. 4.—Kymograph tracing of the effect attending stimulation of the ileocecal valve and sphincter with a rapid tetanizing current. Signal marker lined up with spirometer lever. Inductorium connected in series with signal marker. *1.* Stimulation of terminal ileal opening. *2.* Position 6 cm., electrode in terminal ileum. *3.* Olive tip extruded from terminal ileum. *4.* Olive tip introduced along side of balloon. *5.* Stimulation. *6.* Removal (wave) of balloon from ileocecal valve. *7.* Contraction resulting from introduction of olive tip into medial recess of ileocecal valve between medial frenula and the Elliott applicator. *8.* No reaction. *9.* No reaction. *10.* Reaction after few seconds, likely induced contraction; 4 cm, 10 sec. (counted seconds). (All stimuli timed by Edward A. Boyden.) *11.* Tetanizing current, 4 cm. 12 sec. No reaction. Appears to be refractory. Patient stated that she had vague pain or distress in epigastrium which was not noticed when currents of less than 4 cm. were used. *12.* No reaction, 4 cm. 10 sec. Referred pain to epigastrium. *Removal of bowel content from abdominal wall* resulted in some activity about four minutes after No. 12 stimulus. *13.* Epigastric distress; no contraction, 4 cm. 13 sec. *14.* Removal of olive tip from area of the sphincter. *15.* Point contact on superior lip. Slight evidence of contraction. *16.* Very slight contraction, 4 cm. 10 sec. *17.* Electrode introduced into proximal ileum. *18.* Spontaneous contraction forced balloon out of sphincter. Air cell broken and readjusted. *19.* Electrode placed in the ascending colon. Segmental contractions. Referred pain to epigastric area. *20.* Stimulation of the cecal wall 4 cm. 10 sec. No reaction. *21.* Balloon pulled out of sphincter into the valvular lips.

RESPONSE OF THE EXTRAMURAL TERMINAL ILEUM, ILEOCECAL SPHINCTER, AND ILEOCECAL VALVE TO DRUGS

The generally persistent area of sphincter contraction lay internal to the ileocecal valve (mucosal lips) and at, or slightly distal to, the extramural portion of the terminal ileum and occupied an area of approximately 2.0 cm. in length. A number of drugs commonly used on surgical patients were employed (Table I). Control records of from twenty to sixty minutes were obtained before the drugs were administered.

Morphine Sulfate.—Over a period of seven minutes, .015 Gm. of morphine sulfate was administered intravenously. The patient was asleep thirty minutes later. During this interval the proximal loops showed an increase in tonus and motility. Both segmental and propulsive areas increased in strength and regularity. The terminal ileum, sphincter, and valve showed a decided diminution of motility until the activity present was represented by small segmental waves, with increasing weakness and loss of tonus until at the end of an hour the sphincter was completely relaxed and the ileocecal structure was prolapsed upon the abdominal wall. The sphincter and valve were refractory to mechanical stimuli as repeated stimulation of the cecal wall, the lips of the valve, or the frenula failed to produce a response.

Amyl Nitrite.—The inhalation of 0.3 Gm. of amyl nitrite accompanied by pronounced systemic reaction with depression of the systolic blood pressure was without conclusive effect except in one experiment, when it was used successfully in relaxing a persistent painful segmental spasm of the extramural terminal ileum which followed the injection of 1 c.c. of pituitary extract.

Papaverine Hydrochloride.—Papaverine hydrochloride, .032 Gm., administered intravenously was followed by an increase in activity of the small intestine. Contractions of the sphincter were unaffected during an interval of normal activity, followed by increased motility and tonus.

Adrenalin.—Adrenalin hydrochloride, administered subcutaneously in physiologic doses, abolished all activity of the sphincter and valve and rendered the entire structure refractory to mechanical stimulation. Five experiments in which the general systemic reaction was adequate, and once severe, indicated without exception complete relaxation of the ileocecal valve and sphincteric structure. The extramural portion of the terminal ileum and the proximal ileal loops relaxed with a cessation of segmental and propulsive movements.

Ephedrine Sulfate.—Ephedrine sulfate, .05 Gm., applied to the cecal mucosa of the ileocolic eminence resulted in immediate inhibition of segmental and propulsive action of the valve and sphincter.

Epinephrine Hydrochloride.—Epinephrine hydrochloride, .06 c.c. (1:1000) subcutaneously, suppressed all spontaneous motility of the

intestine, sphincter, and valve. A diminution in tonus was evidenced by marked relaxation of the valve and sphincter during which time the ileocecum was refractory to all stimuli.

Pilocarpine.—Spontaneous activity of the sphincter and the valvular lips was observed for seventy minutes, during which time the motility of the sphincter and lips was generally equivocal. Mechanical stimulation resulted in contraction in both areas. Following the subcutaneous injection of 0.6 c.c. of adrenalin, there was complete cessation of all activity. Twenty minutes later, immediately after the injection of .006 Gm. of pilocarpine, there followed resumption of segmental waves in the valve while the sphincter was somewhat slower to resume activity.

Strychnine Sulfate.—Strychnine sulfate, .002 Gm. dissolved in 2 c.c. water and applied to the cecal mucosa of the ileocecal eminence, inhibited contractions of the sphincter. The experiment was not repeated.

Atropine Sulfate.—Atropine sulfate, .0005 Gm. subcutaneously following the establishment of augmented motility after the injection of 1 c.c. prostigmine methylsulfate, produced an immediate inhibition of propulsive and nonpropulsive activity in the terminal ileum and sphincter.

Prostigmine Dimethyl Carbonic Ester of Oxyphenyl-trimethyl Ammonium Methylsulfate.—One cubic centimeter subcutaneously increased peristaltic activity in the ileum, the proximal small bowel loops, and the sphincter. The increased motility persisted for one to two hours. At another time adrenalin hydrochloride, 0.6 c.c. (1:1000) subcutaneously, resulted immediately in an antagonistic effect on the increased propulsive and nonpropulsive motility of the intestine, sphincter, and valve produced by prostigmine methylsulfate.

Acetyl-Beta-Methylcholine Chloride (Mecholyl).—Twenty-five milligrams intravenously following a forty-minute interval of spontaneous activity resulted in complete cessation of all activity and relaxation of the sphincter. Normal mobility was resumed at the end of four hours.

Pituitrin (Posterior Pituitary Extract).—Pituitrin, 1 c.c. intramuscularly, was accompanied in two experiments by increased propulsive and nonpropulsive activity of the intestine, sphincter, and valve. The patient complained of "gas pains." The response occurred promptly and lasted approximately two hours. On another occasion 1 c.c. of pituitrin was administered intramuscularly after a meal. Propulsive and segmental motility occurred promptly in the three areas, especially the extramural terminal ileum in which a segmental spastic contraction occurred in the area of one balloon lasting twenty minutes producing intense pain. This was relieved after relaxation of the spastic contraction which followed the inhalation of amyl nitrite.

TABLE I

QUALITATIVE AND QUANTITATIVE DATA PERTAINING TO THE ACTION OF DRUGS ON THE ILEOCECAL VALVE, THE ILEOCECAL SPHINCTER, AND THE ILEUM

Frequency of contractions recorded per unit of time in minutes before and after drug

SUBSTANCE	ILEOCECAL VALVE				ILEOCECAL SPHINCTER				TERMINAL ILEUM			
	BEFORE		AFTER		BEFORE		AFTER		BEFORE		AFTER	
	TIME	NO.	TIME	NO.	TIME	NO.	TIME	NO.	TIME	NO.	TIME	NO.
Morphine sulfate	Active		Suppressed		30	7	90	0	Active		Inhibited motility	
Papaverine hydrochloride	Active		Unchanged		60	5	140	19	Active		Increased motility	
Adrenalin	50	4	50	0	50	11	50	1	Active		Inhibited	
Adrenalin hydrochloride	Active		Quiet		70	5	40	0	Active		Reduced motility	
40 min. later: Amyl nitrite	Inactive		Active segmental motility		40	0	60	3	Inhibited		Segmental motility	
Ephedrine sulfate	Active		Inhibited activity		45	5	45	2	Active		Inhibited motility	
Epinephrine hydrochloride	Active		Complete suppression		70	8	130	1	Active		Suppressed motility	
Pilocarpine	50	2	50	30	50	0	50	14	Active		Increased motility	
Strychnine sulfate	Active		Inhibited		40	8	45	5	Active		Inhibited motility	
Atropine sulfate	Active		Inhibited		80	11	75	5	Active		Inhibited motility	
Prostigmine	Active		Augmented		20	2	20	6	20	4	20	11
Mecholyl	Active		Suppressed		40	6	40	1	Active		Suppressed	
Pituitrin	Active		Augmented		45	6	45	13	Active		Evacuation proximal loops	

EFFECT OF DISTENTION OF THE COLON

The sphincter's contractile and segmental activity was inhibited (Fig. 5) during the introduction, and particularly after the distention incidental to a saline enema of 1,500 c.c.

EFFECT OF INCREASED INTRAVESICAL PRESSURE

By means of a balloon residing in the urinary bladder and connected to a mercury manometer and water system, the intravesical pressure was increased without reflux into the ureters. The activity of the valve, sphincter, and ileal loops was reduced (Fig. 6) by increment of the intravesical pressure.[10, 11] Augmentation of activity followed the release of intravesical pressure.

SUMMARY

The factors which determine the state of closure of the ileocecal sphincter such as the pressure of material in the bowel, that is distention, were not operative in this patient as all intestinal content introduced orally was shunted to the exterior through a proximal fistula.

It was observed that retraction or shortening of the ileocecal structure occurs when the segments are coordinated to accept a propulsive wave from an adjacent segment. The ileocecal valve during a propulsive contraction is obliterated by retraction of the frenula and the disappearance of the mucosal folds of the valve as they are retracted over the contracted musculature of the intracecal terminal ileum. A nonpropulsive or segmental wave is not associated with shortening of the active segment and the valve is not obliterated. The ileocecal valve is most readily visualized during periods of inactivity or diminution of tonus in the sphincter area.

The ileocecal valve is generally considered to have a passive mechanical function dependent[12] upon a complete frenulum (type I ileocecal valve was found[6] to occur in 54 per cent of 500 human cecums) and increased intracecal tension whereby the lateral and medial frenula are made taut, closing the arches of the valve. In addition to this adynamic action of the ileocecal mucosal folds, the valve has been shown to be capable of approximation of the lips by muscular contraction (Figs. 1 and 2). Independent contraction of the valvular lips and sphincter resulted by varying the intensity of the stretch stimulus. In addition to the records of contraction the examining finger has been gripped by the mucosal lips.

The observations of Wesson,[13] and White and associates[5] were confirmed as to the presence of a definite contracting muscular band within the cecal portion of the terminal ileum proximal to the mucosal lips. Boyden examined this area and suggested it may be located in the aperture of the colon where the ileum passes through the cecal wall. When contracted the intestinal lumen completely excludes the introdue-

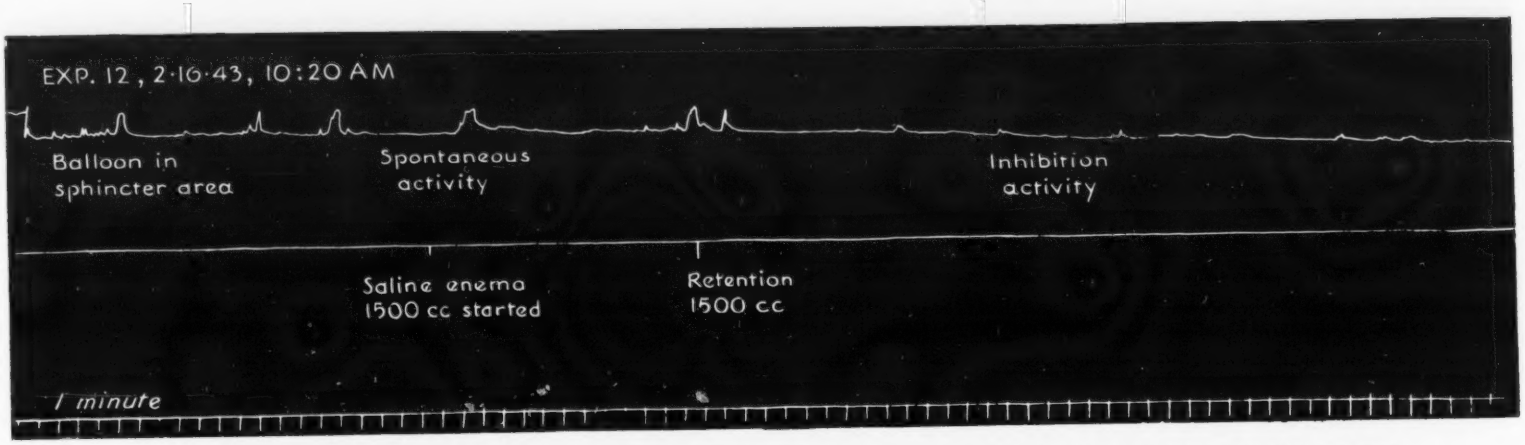

Fig. 5.—Kymograph tracing illustrating the inhibition of the ileocecal sphincter following increased intracolonic pressure.

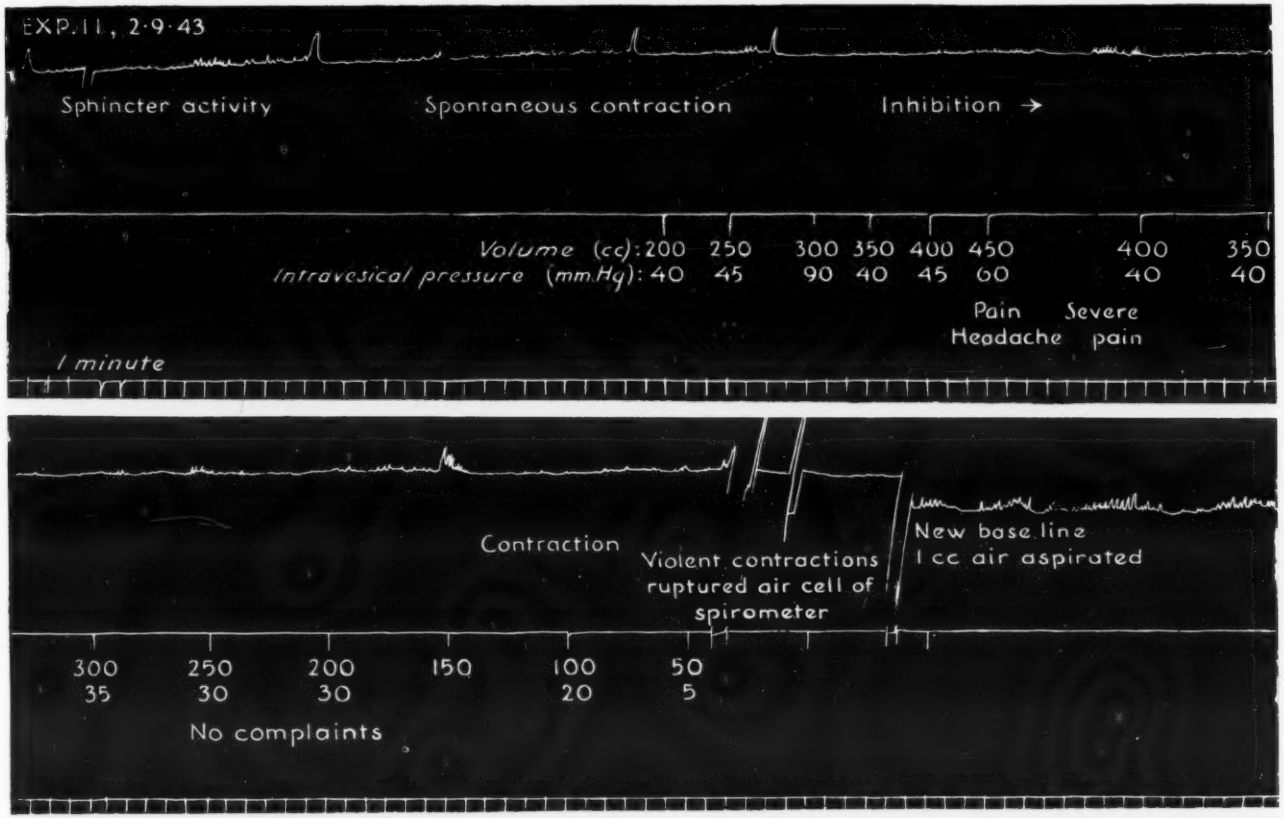

Fig. 6.—Kymograph record of the effect of increased intravesical pressure on the motility of the ileocecal valve and sphincter. Signal marker and spirometer lever were synchronized. The bladder was distended at the rate of 15 c.c. per minute. Inhibition occurred when 300 c.c. or a vesical pressure of 90 mm. Hg was obtained. This pressure was momentary and quickly dropped to 60 mm. Hg. Activity was not completely suppressed. Inhibition lasted for forty-five minutes when a spontaneous contraction occurred. As the bladder was emptied a violent series of contractions ruptured the air cell of the spirometer. Subsequently the activity became steady but less vigorous. During the period of inhibition, quiescence of the proximal ileal loops persisted.

tion of an instrument beyond the sphincter without a force far exceeding the pressures found by Wangensteen[14] and Sperling[15] within the colon in cases of colonic obstruction. Rutherford, White and co-workers, and Wesson have mentioned the difficulty of forcing the sphincter from the cecal side. An opportunity to determine the resistance of the sphincter from the ileal as well as the cecal side was overlooked in this study.

The inhibitory effect of increased intraluminal tension, intracolonic and intravesical pressure, upon the contraction of the sphincter may upon occasion be one of the physiologic factors underlying incompetency of this junction when the type of ileocecal valve due to its variable structure would not justify an expectation of competency.

The reports of others[7, 16, 17, 18] have repeatedly indicated the species difference of the reaction of the sphincter and valve to adrenergic substances. The reaction of the human ileocecal valve and sphincter following the injection of epinephrine-like substances and other drugs justifies the assumption that these structures behave not unlike the small intestine. Wesson[13] and I[19] agree that the presence of an extracircular muscle in a large number of embryonic and adult specimens of the intracecal terminal ileum was not observed upon microscopic examination of innumerable serial sections.

CONCLUSIONS

Experimental results indicate that the mechanical, hormonal, and local reflexes of the ileocecal valve and sphincter are so adjusted as constantly to produce responses identical with those of the small intestine to adrenergic and cholinergic drugs.

The balloon method of investigation failed to reveal any fundamental distinctions in the behavior of the ileocecal valve, the ileocecal sphincter, and the small intestine.

The apparent similarity of activity in the extramural terminal ileum, sphincter, and of the intracecal terminal ileum and the ileocecal valve gives rise to the need for further interest in the physiology of this area.

The presence of an area of increased contractility was observed within the cecal portion of the terminal ileum.

Prolonged tonic contractions, characteristic of sphincter action, were not observed.

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PAPILLOMA OF THE GALL BLADDER

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IN REVIEWING the literature on the subject of papilloma of the gall bladder one is immediately impressed with the diversity of opinion as to the occurrence of this pathologic entity.

Kerr and Lendrum[1] in their extensive review of the subject concluded that but twenty-one "authentic" cases had been found up to 1936. Yet, one writer alone, Phillips[2] reported 500 cases of one or more papillomas found in an unstated number of gall bladders removed at the Mayo Clinic in a period of six years from 1923 to 1929. Shepard and associates,[3] in a report on gall bladder tumors in general in 1942, reported forty-five cases under the heading of polypi, which from their pathologic description probably were mostly papillomas. These cases were a collection of the three authors over a period of thirty-two years from 1906 to 1938. Kirklin[4] reported in 1931, that the incidence of papillomas was about 8.5 per cent in more than 1,700 gall bladders removed at the Mayo Clinic over a period of seven years. This publication covered the same period as that of Phillips[2] of the same clinic and shows a marked statistical variance. Kirklin[5] also reported, in 1932, fifty-one cases diagnosed roentgenographically of which fifteen were treated surgically and fourteen were pathologically demonstrated to be papilloma.

In a casual survey among surgeons of my acquaintance and from the records of the hospitals with which I am connected, a single incidence or no knowledge of a single case of this pathologic entity could be recalled. Within a period of six months two such cases have come under my care and were diagnosed preoperatively as papillomas of the gall bladder.

CASE 1.—H. T., a 46-year-old white woman, complained of pain in the right upper quadrant one-half to four hours after meals, particularly after fried or fatty foods had been ingested. Loss of twenty pounds in weight was also reported. The patient was a tripara who was in excellent health up to three years before admission when, because of menorrhagia due to uterine fibroids a hysterectomy had been performed. Following this, surgical menopause associated with moderately discomforting climacteric symptoms occurred. Estrogenic therapy was instituted and the patient was in good health until the initial attack of upper right quadrant pain. About six months before admission the patient had a severe attack of colicky pain in the right upper quadrant radiating around the upper abdomen and backward toward the right scapula. This was accompanied by nausea and vomiting. A physician administered morphine, which relieved the attack. However,

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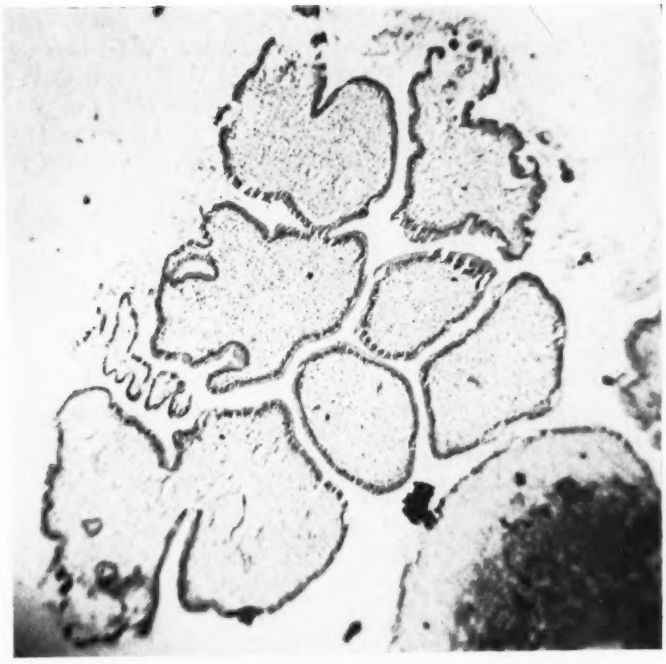

Fig. 1.

Fig. 2.

since that time the ingestion of fatty and fried foods caused bloating, sour eructations, and belching. Appetite was poor because of fear lest eating precipitate an attack.

Examination showed apparent loss of weight, slight epigastric tenderness, and midline low abdominal scar. Examination was otherwise essentially normal.

There were no abnormal urinary findings. Hemoglobin was 82 per cent; erythrocytes, 3,800,000; leucocytes, 7,600; polymorphonuclears, 62 per cent (58 per cent segmented and 4 per cent stab); lymphocytes, 35 per cent; monocytes, 2 per cent; eosinophiles, 1 per cent. Gastric analysis showed no free acid in fasting specimen. There was marked hypochlorhydria by the fractional method (Ewald meal), free hydrochloric acid reaching maximum 10 degrees at forty-five minutes, and no abnormal microscopic findings.

Fig. 3.

Gall bladder series reported by Dr. Frederic Betelheim showed a normal sized and shaped gall bladder, well visualized. There was a small negative shadow remaining in the same relative position in all views. Emptying was slightly delayed. This negative shadow was thought to be a stone or a papilloma. Because of the consistently fixed position of this shadow the latter was considered more likely. Gastrointestinal series revealed no pathology.

Upon operation March 18, 1943, a small thin-walled gall bladder was found which emptied itself easily upon pressure. No stones or growths could be palpated within the fundus. The common duct was explored and revealed no pathology. No other intraabdominal abnormality was seen. Because of the symptomatology and x-ray findings the gall bladder was removed. When opened and

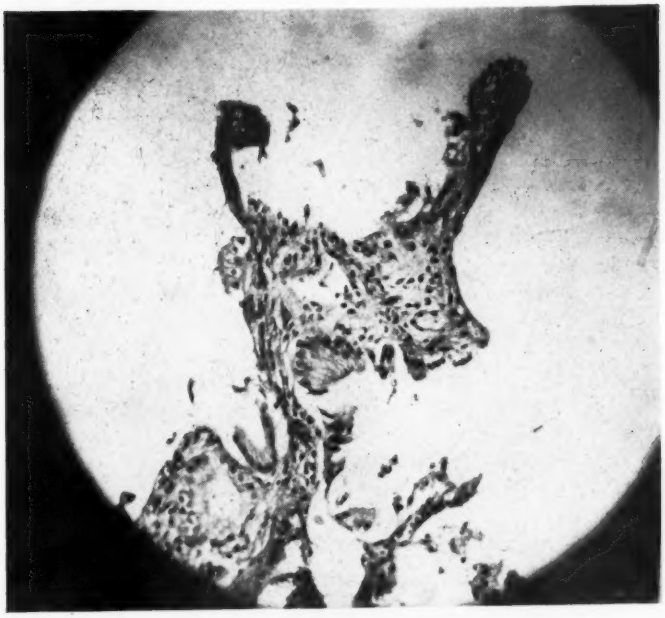

Fig. 4.

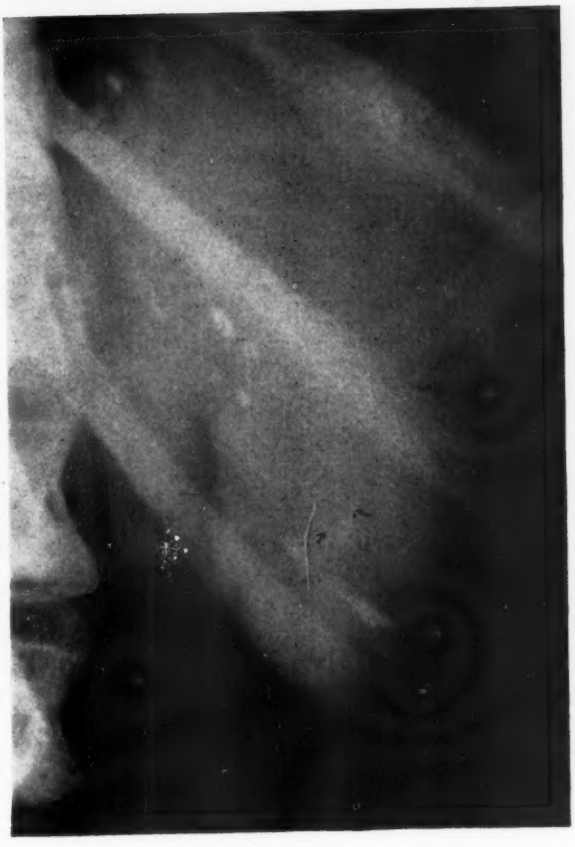

Fig. 5.

examined, a pea-sized papilloma was found in an otherwise apparently normal gall bladder. The pathologic report on the specimen submitted was as follows:

Gross examination showed a gall bladder 5 cm. long by 1½ cm. wide at midportion. The thickness of the wall averaged 1 mm. The mucosa was diffusely reticulated and there was at the fundus a papilloma the size of a split pea.

Microscopically, the histologic picture presented an edematous fibrous tissue core covered by a layer of low columnar epithelium. At times, continuous papillomatous stalks came together and produced a picture of adenoma. The structure of the individual papillomatous stalks is best seen when cross sections of a few of them are represented in a microscopic field.

The postoperative course was uncomplicated. On subsequent examination the patient's appetite had returned to normal with gain in weight and no further food idiosyncrasies.

Fig. 6.

Case 2.—R. K., a 36-year-old white married nulliparous woman, complained of slight discomfort after eating. About one week previous to examination the patient had a severe colic in the right hypochondrium accompanied by nausea and vomiting.

The patient had had the usual childhood diseases. Otherwise she had been fairly well except for an attack of appendicitis about eight years before admission for which appendectomy was performed. Following this the patient suffered from constipation and vague gastrointestinal complaints. An operation for "adhesions" was performed about three years before admission, after which the patient stated she felt fairly well except for an occasional attack of indigestion.

About one week previous to admittance the patient had a severe attack of pain in the right upper quadrant. A physician diagnosed the condition as an acute gall stone colic and administered morphine which relieved all symptoms. The patient was referred for surgery with a diagnosis of cholecystitis with cholelithiasis.

Physical examination was essentially negative and blood count, blood chemistry, and urinalysis were normal.

Examination of the x-ray pictures submitted showed a small negative shadow in a well-filled gall bladder which was slightly larger than normal. The gall bladder emptied fairly well after a fatty meal and the negative shadow persisted. The negative shadow was reported as a single stone. However, because of the relatively fixed position of the shadow in all views, a diagnosis of papilloma of the gall bladder was made.

Upon operation, Aug. 2, 1943, numerous adhesions were found although the gall bladder itself was fairly free except for a few small bands between the fundus and the hepatic flexure of the colon. The gall bladder emptied itself easily, was thin-walled, and no stones were palpated within it or in the biliary passages. The organ was removed in spite of its normal appearance because of the roentgenographic findings and previous history of colic. Upon opening the gall bladder a small papilloma was found in the fundus and the mucosa showed a typical picture of the strawberry gall bladder.

Pathologist's report.—Pathologic examination of the gall bladder showed a pear-shaped gall bladder 6½ cm. long and 3½ cm. wide. The organ had been turned inside out and the mucosa presented a typical strawberry appearance. The wall was edematous and averaged 3 mm. in width. A papillomatous mass the size of a split pea was present on the mucosa. There were no stones.

Microscopically the picture was that of a chronic cholecystitis with a localized papillomatous excrescence. The latter consisted of a layer of epithelium from the mucosa of the gall bladder, investing a core of clear cells filled with lipoid.

The postoperative course was uncomplicated and subsequent examination showed the patient to be in excellent health and symptom free.

DISCUSSION

In most of the literature reviewed the question of malignancy of papilloma is raised in view of our knowledge that these same tumors occurring in the urinary bladder or gastrointestinal tract very often so manifest themselves. However, except for one case of associated malignancy reported by Phillips,[2] which he believed to be concomitant rather than resultant pathology, no such tendency is noted.

An also singular conclusion reached by most writers is that whereas carcinoma of the gall bladder is usually associated with cholelithiasis, papillomas rarely show such tendency. However, Phillips[2] mentioned stones found in his cases but by his reference to MacCarty's description of "Cholecystitis Catarrhalis Papillomatosis" his cases probably included many of this description.[6] Probably this latter pathologic condition would be found in most acute or acute exacerbations of chronically affected gall bladders. However, this communication is concerned with papilloma occurring as a single tumor or multiple tumors which are not associated with other or only slight pathology. Kirklin[5] pointed out that most of the gall bladders in which he was able to demonstrate papillomas proved, upon subsequent examination after removal, to show only slight or no other concomitant pathology.

As for the pathologic picture itself, probably the best description is that of Ringel,[7] who described the true papilloma of the gall bladder as a framework of vascular connective tissue covered by a single layer of tall columnar epithelium. The tumor may be sessile or pedunculated, measuring from 1 to 5 mm. in diameter. Occasionally clear cells containing refractile neutral fat or cholesterin are found in the connective tissue core.

Symptomatically these patients present a picture simulating any type of gall bladder disease from the simple occasional biliary colic to severe obstruction with jaundice.

Brown and Cappell[8] described a case of chronic obstructive cholecystitis with multiple papillomas. Henry[9] described a case of papilloma of the gall bladder in which a papillary implant was found in the cystic duct. Symptoms of slowly progressive obstruction necessitated operation at which multiple villous papillomas of the fundus were also found.

Another point for conjecture is whether we may not tend to overlook this pathologic entity owing to the failure of visualization of the growth in the roentgenographic picture.

Even at operation it is possible to overlook this pathology as proved by the two cases cited, as the gall bladders in both cases were so normal in appearance, to palpation, and, in response to emptying on pressure, that it was with some reluctance that cholecystectomy was performed.

CONCLUSIONS

1. Papilloma of the gall bladder is a rather rare occurrence.
2. Papilloma of the gall bladder may simulate any type of biliary disease.
3. The diagnosis of papilloma of the gall bladder preoperatively can be made only upon roentgenographic study.
4. At operation the gall bladder may appear absolutely normal but should be removed if symptoms of biliary disease were clinically present and if at operation no other intra-abdominal pathology can be found to account for the symptomatology.

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THE UROBILINOGEN TEST AS AN ADDITIONAL AID IN THE EARLY RECOGNITION OF FECAL FISTULA

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AN EXTERNAL colonic fistula is an abnormal communication between the colon and the surface of the body. Such fistulas are called fecal fistulas because they communicate with the colon and discharge intestinal contents and feces. Most of these colonic fistulas are postoperative, only a few occurring spontaneously.

The diagnosis is usually made by the ingestion of aniline dyes, such as Congo red, and the subsequent appearance of these dyes in the discharges. It is the purpose of this article to show how the Ehrlich test for urobilinogen may be used to establish further the diagnosis of a fecal fistula.

The term "urobilin" was first used by Jaffe in 1868.[1] While spectroscopically studying the oxidation products of bilirubin, he noted an undescribed absorption band at about 490 to 500 millimicrons. Because of its occurrence in urine and bile, he called the substance giving this absorption band, urobilin. Van Lair and Masius,[2] in 1871, described a similar pigment in the feces which they called "sterocobilin." In 1901, Ehrlich[3] described a color reaction in urine with concentrated hydrochloric acid and p-dimethylaminobenzaldehyde. Neubauer,[4] in 1903, noted that fresh urine gave a positive Ehrlich reaction, but no urobilin absorption spectrum. On standing, as the Ehrlich reaction became weaker, the urobilin absorption spectrum became progressively stronger. He also showed that the reduction of noncrystalline urobilin with sodium amalgam yielded a chromogen with a strongly positive Ehrlich reaction. Bauer,[5] in 1905, reduced bilirubin obtained from cattle gallstones with sodium amalgam. The resulting chromogen gave a strongly positive Ehrlich reaction, thus demonstrating further the relationship of bilirubin, urobilinogen, and urobilin. Le Nobel[6] as early as 1881 had made studies of this chromogen and called it "urobilinogen." Friedrich Von Mueller[7] in a classical experiment demonstrated the enterogenous origin of urobilin and its enterohepatic circulation. He fed hog bile to a patient with a complete biliary obstruction. On the second and third days, respectively, urobilin appeared in the feces and then in the urine. The experiment was then repeated with urobilin-free bile and the same results obtained. Mc Master and Elman[8] many years later confirmed these results. The hepatogenous theory of the origin of urobilin, of which the French workers were adherents, has practically been abandoned. Meyer-Betz[9] points out the fact that although disproved, the hepatogenous theory

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continued to hold the interest of these men for at least two decades. Gerhardt,[10] in 1897, described the occurrence of urobilinogen in pleural, pericardial, and peritoneal exudates. The bacterial reduction of bile pigments to form urobilinogen has been demonstrated by various observers. Von Mueller[7] showed that on standing, bile bilirubin decreased and the bile urobilin increased. Maly,[11] and Kammerer and Miller[12] showed that one may produce urobilin in vitro by inoculating sterile urobilin-free bile. McMaster and Elman[8] have been able to accomplish the same in vivo, by putting particles of stool into the previously sterile biliary tracts of dogs.

Fischer[13] gave us the first concrete knowledge of the chemistry of this group of substances. He showed that bilirubin was converted by simple reduction to mesobilirubinogen, which on exposure to light and air gave urobilin characteristics. It remained for Watson[14-17] to isolate crystalline stercobilin from both human feces and pathologic human urine. He then demonstrated that crystalline urobilin prepared from mesobilirubinogen differed from stercobilin in a number of respects.[18, 19] Siedel and Meier[20] then synthesized this compound and called it urobilin IX a. Human bile samples that are reduced with amalgam result in urobilinogen which upon conversion yields urobilin IX a.[21] Watson, Sborov, and Schwartz,[22] in determining whether stercobilin is derived from mesobilirubinogen, have recently shown that the output of stercobilin is greatly increased in the feces when mesobilirubinogen was given by mouth. It is reasonably certain that this conversion of mesobilirubinogen to stercobilin is probably related to bacterial action. An interesting advance was made recently by Watson and Schwartz[23] who showed that on addition of bile and mesobilirubinogen to acholic feces, one may cause stercobilin formation in some feces, and a dextrorotatory urobilin in others. Normal stercobilin is levorotatory, and this knowledge added to the finding that d-urobilin may be obtained in infected bile samples to which mesobilirubinogen has been added indicates that some unknown factor may influence the direction of conversion.[24] Previously, Watson[25] had shown that the color intensities of mesobilirubinogen-aldehyde and stercobilinogen-aldehyde, as developed by his modification of Terwen's method, were identical.

With this in mind it was thought that the Ehrlich reaction, which is given by mesobilirubinogen and stercobilinogen, might be used in suspected cases of fecal fistula. To 2 or 3 c.c. of the discharge of the suspected fistula in a test tube, an equal amount of Ehrlich's reagent (p-dimethylaminobenzaldehyde) was added. Two volumes (to one of the material being tested) of a saturated solution of sodium acetate were then added.[26] A pink to red color indicated the presence of an urobilinogen.

This procedure was used on the following cases:

Case 1.—E. N. (University Hospital No. 732750) had had a resection of a tumor of the colon which had extended into the bladder. This necessitated resec-

tion of the colon and partial resection of the bladder including division and ligature of the left ureter. Penrose drains were inserted. Postoperatively her course was rather stormy. Much discharge was observed from the drains. A question arose as to whether there may be a urinary fistula, a fecal fistula, or both. Five cubic centimeters of the discharge were tested for urobilinogen, and a positive reaction was obtained. The urine showed no urobilinogen. While this did not eliminate the possibility of urinary fistula it was evident that fecal contents were present. Congo red was ingested and was observed the next day on the dressings, further establishing the presence of fecal fistula. At post-mortem examination, eleven days after operation, communications were seen to exist between the external skin surface where the drains had been placed and the bladder and colon.

CASE 2.—H. S. (University Hospital No. 732767) also had a colon resection for tumor. The discharge of drainage areas was again tested and a positive urobilinogen test was obtained. On post-mortem examination a fecal fistula was found.

CASE 3.—MRS. H. S. (University Hospital No. 734917) had a resection of a segment of ileum for closed loop obstruction occasioned by a perforation of an ulcerative enteritis. Postoperatively the skin wound broke down and a purulent discharge was obtained. The possibility of a fistula was entertained. However, the test for urobilinogen and bilirubin was negative on some of the exudate. Congo red was given and was not observed on the dressing. On post-mortem examination no fistula was found.

COMMENT

Although we have not used the Ehrlich test in cases of small bowel fistulas, it would seem that the Gmelin color play with yellow nitric acid might be used on discharges in addition to the Ehrlich test. Bilirubin, mesobilirubin, and biliverdin will give a positive Gmelin reaction. The Ehrlich test will be positive if there is any urobilinogen present. No reference has been found in the literature to the use of these tests in cases of intestinal fistulas.

In the case of a colonic fistula wherein the jaundice is due to a complete, unremitting obstruction such as carcinoma of the head of the pancreas, the Ehrlich test would probably not be of any use. Such a combination would be most unusual, however.

The value of the testing of discharges of fecal fistulas would be in the following:

1. Early recognition, that is, the examination of a material already escaping from the wound as contrasted with the observation of escape of material from the wound only after ingestion of charcoal or Congo red.

2. In the presence of intestinal paresis, the delay in transit would not invalidate the test, as it may with charcoal and Congo red.

SUMMARY AND CONCLUSIONS

The Ehrlich test for urobilinogen is suggested as an additional diagnostic aid in the diagnosis of external colonic (fecal) fistulas. Three

cases are presented, in two of which the findings were corroborated by autopsy findings, and in the third a negative test was also confirmed by absence of fistula at autopsy.

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ACUTE PHYSIOLOGIC RESPONSES IN EXPERIMENTAL HEAD INJURY WITH SPECIAL REFERENCE TO THE MECHANISM OF DEATH SOON AFTER TRAUMA

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IN TWO previous communications,[12, 19] the subject of experimental head injury was discussed and the salient points concerning vital functions were brought out. In this report are considered in greater detail the changes of blood pressure, pulse, respiration, the conscious state, and reflexes in acute trauma. The mechanism of death soon after trauma will be analyzed. The changes to be described are seen immediately following the trauma and should not be confused with the manifestations of vital functions in more chronic forms.

METHODS AND MATERIALS

Mongrel dogs, weighing between 7 and 15 kg., were used for these experiments. Morphine analgesia was used in quantities of 20 mg. per kilogram of body weight. The drug was administered subcutaneously. When operative procedures were necessary, intravenous nembutal anesthesia was used. The exposure of vessels was done under ½ of 1 per cent procaine infiltration anesthesia.

The blood pressure was recorded from the femoral artery, respirations by means of a balloon about the thorax. The cranial trauma was administered by means of a hammer, falling weight, striking object propelled by a spring pendulum, and by shooting. Except in the case of the hammer, the velocity and the force of the striking object were controlled. The head injury was delivered after exposure of the bone by reflection of the scalp and the underlying masseter muscles.

A number of preparations were made prior to injury. In two animals the spinal cord was sectioned at the first thoracic segment twenty-four hours before the injury was delivered. In three animals the adrenal glands were removed before injury. In five animals the vagus nerves were cut and the carotid arteries ligated and sectioned. In three animals yohimbine was administered intravenously in order to remove the influence of the sympathetic nervous system by chemical means. After the administration of the drug, if intravenous adrenalin did not in-

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fluence the blood pressure, the animal was thought to be well yohimbinized. In three animals, bilateral supratentorial exposure of brain was made before injury by bullet. In nine dogs correlations were made between changes in medullary function and the electroencephalographic findings. The animals were prepared by first inserting electrodes in both parietal regions on either side of the midline. Before, during, and after trauma, an attempt was made to record the electrical activity of the brain.

ACUTE PHYSIOLOGICAL RESPONSES

Irrespective of the method of injury, the acute responses are divisible into three types: (1) minimal, (2) moderate, and (3) profound. In the group with minimal response, there was, as a rule, on change in blood pressure, pulse, or respiration. The blood pressure rarely showed an increase at the time of the blow. In this group the lid reflexes were normal and the animal was in excellent condition; his chances of survival were excellent. However, in one instance there was hypertension with respiratory pause in a conscious animal and in another only hypertension occurred, with normal respirations and normal conscious state.

Among the animals with moderate response, there was a short period of unconsciousness, evidenced by inability to respond to painful stimuli. Hypertension usually occurred immediately following the blow. This lasted 60 to 120 seconds. There was an associated tachycardia which usually disappeared within 40 to 80 seconds. In an occasional case vagal stimulation, as evidenced by decreased pulse rate and subsequent escape, occurred. The respirations were very rarely increased (Fig. 1), indeed, an apnea usually occurred which lasted from 10 to 40 seconds with later return to normal. The majority of these animals would survive the injury. The corneal reflex was lost usually for several seconds. In a few instances, the animal became irresponsive to pain without loss of reflexes. In one example, the blood pressure dropped immediately following trauma and eventually became restored to its original level. Respirations which had stopped for 70 seconds were resumed (Fig. 2).

Among those animals with profound effect, the picture was typical in almost every instance. The animal was unconscious. There was a sudden sharp rise in blood pressure at the instant of trauma averaging between 75 and 125 mm. of mercury (Fig. 3). Slowly the blood pressure dropped, in many instances to zero at the end of 3 to 6 minutes. In Fig. 2, a secondary rise interrupting the steep blood pressure fall is attributable to medullary anemia. In a few cases, after an initial drop, a new increase in pressure appeared, associated with renewed respirations. But eventually, even though there were spontaneous respirations, the blood pressure failed and death ensued. In one instance, a profound effect obtained without increase in the pressure. In another

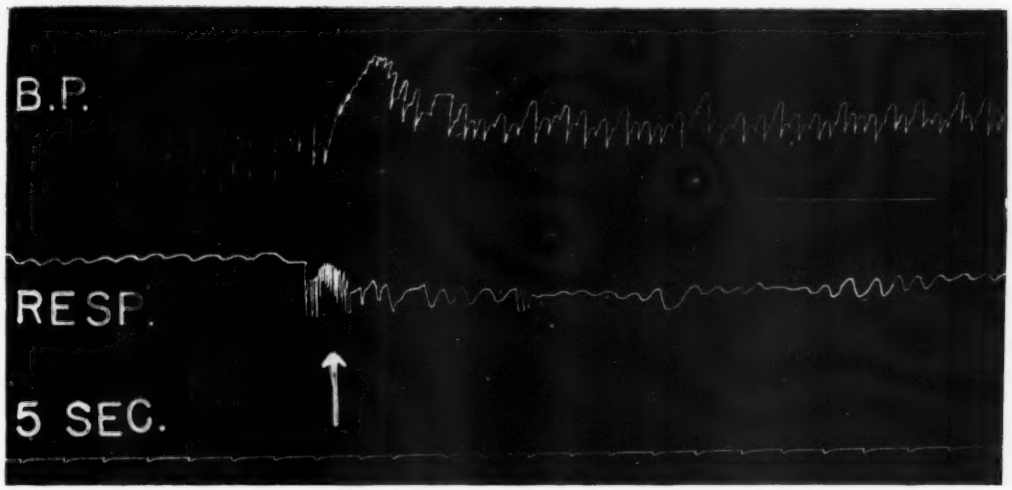

Fig. 1.—An example of increased respirations and vasomotor activity with lost corneal reflexes. Dog 30 was administered a single hammer blow to the right parieto-occipital region of the head. Corneal reflexes were lost for 29 seconds. There was a steep rise of blood pressure and stimulation of respirations lasting 7 seconds. The dog had no fracture of the skull. There were contusions of the base with moderate hemorrhage. It would have survived the injury.

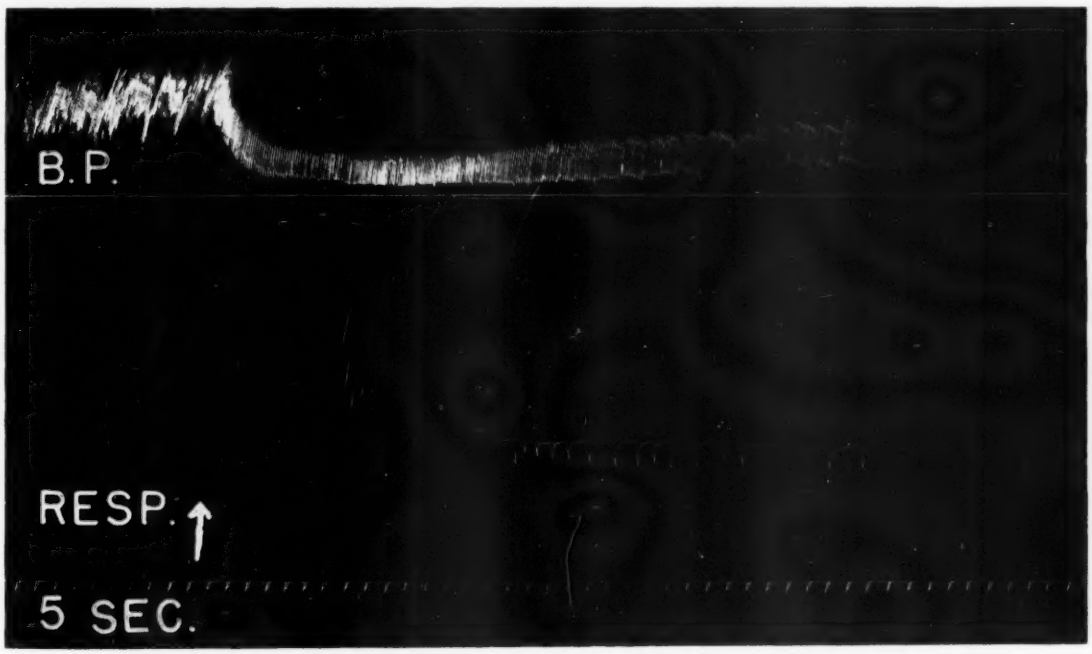

Fig. 2.—An example of a drop in blood pressure in a moderately injured dog. Dog 158 was injured with the pendulum. There was a drop in blood pressure with bradycardia. The blood pressure slowly rose to its original level with the animal carrying on satisfactorily. Respirations became regular at the end of 70 seconds. A large area of depression with extrusion of the brain was obtained. There was severe laceration of the left parieto-occipital cerebrum and the superior surface of the cerebellum. Cross sections of the brain stem and spinal cord revealed many areas of punctate hemorrhage. In the spinal cord there was a large, 2 mm. hemorrhage about the central canal. Small punctate hemorrhages were also present.

Fig. 3.—An example of profound effect characterized by pressor response, respiratory paralysis, initial spasticity with neck retraction followed by stilling within two minutes. Note the initial steep rise of blood pressure (110 mm. Hg) followed by a steep fall. The fall is interrupted by a secondary rise in pressure, most probably due to medullary anemia. Artificial respirations were of no avail. This animal had been hit upon the head the day previously, with a moderate response. This record was obtained after a blow to the left occipitoparietal region.

case, the blood pressure dropped with complete failure. The pulse increased remarkably with the blow, and this increase was sustained to the end. In a few instances there was vagal inhibition followed shortly by escape. The respirations invariably stopped and in some cases there was sufficient recovery for spontaneous respiratory movements followed by failure. All animals in the profound group either died within a few minutes after the beginning of the experiment or within an hour or two if not sacrificed. Associated with changes in the vital functions there was almost always a lost corneal reflex. In some animals the corneal reflex returned to disappear again in a short time. However, in one example, a profound effect was obtained and yet reflexes were active almost to the last. In the moderately and severely injured animals generalized rigidity with extension of limbs and retraction of the head and neck was seen frequently, followed by limpness within a short time.

Fig. 4.—An example of head injury in an adrenalectomized animal. In Dog 175 both adrenal glands were removed under nembutal anesthesia. The corneal reflexes were present before injury. A right parieto-occipital hammer blow caused a profound pressor effect (100 mm. Hg) with loss of respirations for 40 seconds. They returned for 120 seconds, followed by final loss and death of the animal. There was marked tachycardia and a steep fall of blood pressure following the initial rise.

Section of Both Vagi and Carotid Arteries.—A section of both vagi caused a marked increase in the pulse rate associated with a moderate increase in the blood pressure which became normal again within ½ to 1 hour. In the group of animals in which the vagi and the carotid arteries were sectioned, injury to the head caused responses similar to those seen in the intact animal except that there was no change in the pulse rate.

Adrenal Influence.—These animals were prepared twenty-four hours previously by removal of both adrenal glands under nembutal anesthesia. The head injury was administered under morphine analgesia. The injury in this group caused the usual rise in the blood pressure associated with respiratory failure (Fig. 4). It was believed that the increase in blood pressure in this group of head injury experiments was not mediated by a humoral factor (adrenalin liberation).

Sympathetic Influence.—Several animals were prepared twenty-four hours previously by section of the spinal cord at the level of the lower cervical segment under nembutal anesthesia. The injuries were administered under morphine analgesia (Fig. 5). These animals had a low blood pressure following the spinal cord section. Several blows to the head with eventual profound effect were never associated with hypertension. It seems reasonable to assume that if the spinal cord had been intact, there would have been the usual acute hypertension ordinarily associated with trauma.

Fig. 5.—An example of head injury after section of lower cervical spinal cord. Dog 180 was prepared by section of the spinal cord at the lower cervical level under nembutal anesthesia. He was allowed to recover overnight, and on the following day hammer blows were administered on the right parieto-occipital skull under morphine analgesia. The accompanying figure shows the aftereffects of the fourth blow. A compound fracture with lacerations and contusions of the brain was produced with hemorrhage at the base. The reflexes and respirations were lost immediately. Respirations returned in 90 seconds and disappeared again 70 seconds later. At one point there was a marked vagal effect. The animal died.

The use of yohimbine as a sympathetic paralyzing agent was instructive (Fig. 6). When the animal was given a sufficient amount of yohimbine and when its blood pressure could not be raised by injection of ¾ c.c. of adrenalin solution, injury to the head was never associated with increase in blood pressure. These two groups of experiments suggest that the sympathetic nervous system mediates the acute peripheral hypertension in head injury.

Head Injury After Bilateral Craniotomy and Exposed Brain.—In several animals the cranial cavity was opened on both sides. The dura was incised and reflected to expose the brain. Under these conditions

a supratentorial bullet wound never caused a pressor effect even though three out of four animals were mortally wounded. In each instance there was marked laceration and dissolution of brain tissue. The respirations were lost in two instances with no return. In one there was no loss of respirations, and in another they waxed and waned on several occasions.

The lack of a pressor effect in these experiments is another argument proving that the increase in the blood pressure is brought about by medullary stimulation and could not be caused by stimulation of supratentorial cortical or subcortical centers. This was also proved beyond doubt by Polis[17] and Denny-Brown and Russell[3] in decerebrate preparations. In such animals, the pressor effect was obtained after adequate blows to the head even though connections with higher centers were disrupted.

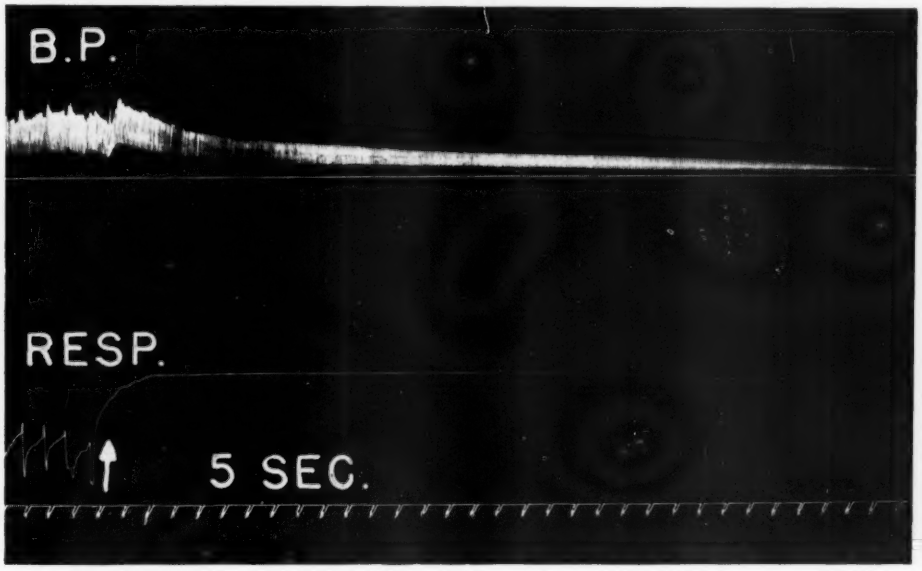

Fig. 6.—Yohimbine experiment. Dog 181 was given 2 c.c. of yohimbine, intravenously (1 per cent solution) to abolish the sympathetic nervous system response. The blood pressure fell, but the heart rate remained about the same. Ten minutes later another cubic centimeter of yohimbine was given. Three minutes afterward ¾ c.c. of 1 to 1,000 adrenalin solution injected intravenously caused tachycardia, but no change in blood pressure. It was now assumed that the dog's sympathetic nervous system was well neutralized. The dog was hit a heavy blow over the occiput. There was no change of reflexes or respirations, or rise of blood pressure. The dog was struck a second time with profound effect. Reflexes and respirations were abolished. There was no rise in blood pressure and it fell to zero within a few minutes.

Effects of Injury of Medulla and Upper Spinal Cord on Vasomotor and Respiratory Centers.—In four animals the medulla or spinal cord was injured by gunshot. In two instances injury was at the obex, in one 5 mm. below the obex, and in another 5 cm. down the spinal cord. In the two dogs where the neighborhood of the obex was destroyed by a .22 caliber bullet, the pressor effect did not appear (Fig. 7). In the animal with injury a little below the obex, there was a marked pressor response

(Fig. 8). In the fourth animal with injury lower down the cervical spinal cord, there was no change in the systolic blood pressure but the pulse pressure increased markedly (Fig. 9).

These results differ from those obtained by Polis,[17] who stated that injury to the vasomotor centers or the cervical spinal cord uniformly causes hypertension. The dissolution of the vasomotor centers by injury should, theoretically at least, cause no pressor response, whereas a lesion lower down or higher up may stimulate the center as in other forms of head injury.

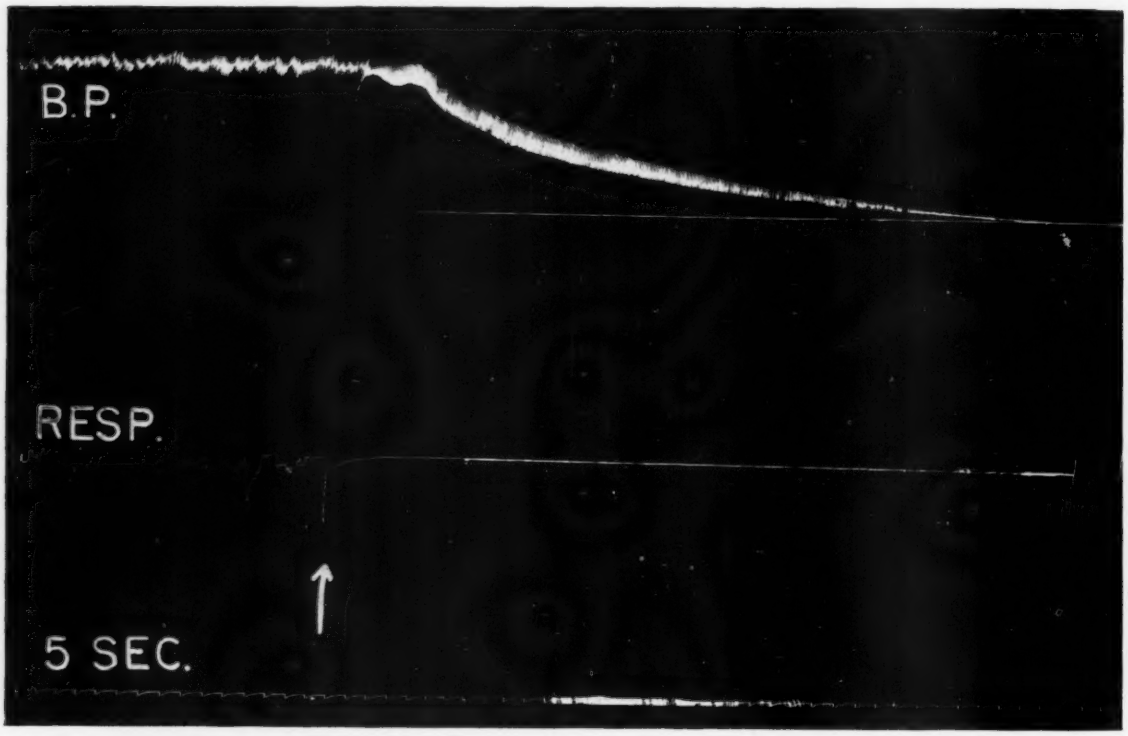

Fig. 7.—An example of a bullet wound of the vasoconstrictor center with no initial pressor response. In order to injure the medulla more accurately, Dog 108 was prepared by exposing the atlanto-occipital neighborhood under morphine analgesia and procaine infiltration. The closed-cavity hydrodynamics of the head were not disturbed. The medulla was then shot with a .22 caliber bullet, with profound effect but no rise in blood pressure. There was cessation of respirations and loss of corneal and lid reflexes. Autopsy revealed an injury in the neighborhood of the obex.

Electroencephalographic Correlations.—A study was made of the changes in the electrical activity of the cortex at the time that evidences of medullary involvement were present. In a number of the animals with profound effect and lost corneal reflexes the electrical activity of the cortex in the parietal region continued unaltered. In others the activity of the cortical surface became impaired with little or no change in medullary functions. It was felt that in the latter group a more direct injury to the cortex was brought about by the trauma and a consideration of the former suggested that a blow to the head might be

severe enough to cause medullary involvement without at the same time upsetting the electrical activity of the surface of the brain. In most experiments recording of the brain waves was resumed within 3 to 6 seconds after the blow and even though the changes during this period are unknown, the evidence points to selective involvement of the nervous system. That is, in some animals or at certain times in the same animal, there was greater involvement of medullary centers than of the cortex. In other animals, and at times in the same preparation, the medullary centers were spared and there was marked involvement of the cortex (Figs. 10 and 11).

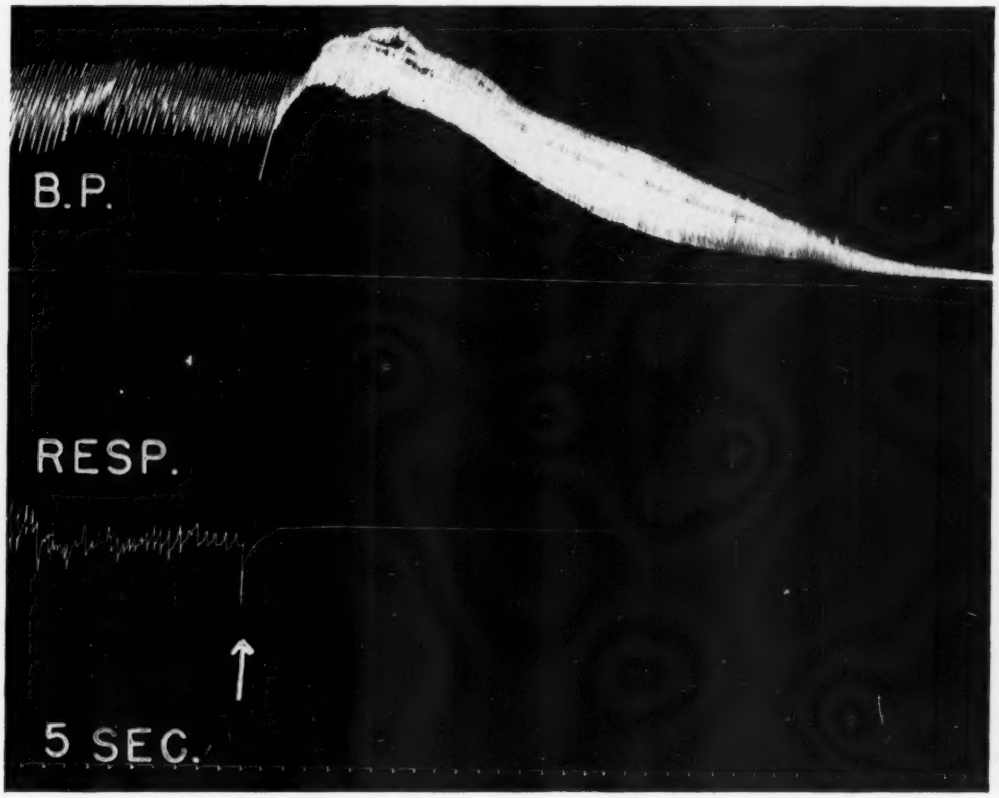

Fig. 8.—An example of injury of the spinal cord a few millimeters below the obex with a pressor effect. Dog 103 was injured by shooting at the neck with a .22 bullet in an attempt to injure the medulla. A remarkable rise of blood pressure with tachycardia and progressive failure associated with lost respirations and reflexes were obtained. Autopsy revealed that the bullet had entered a fingerbreadth below the obex. There were bruises and contusions of the frontal lobes suggesting transmitted energy throughout the closed skull cavity.

In Fig. 10, the electroencephalographic findings following a single fatal blow are shown. It can be noted that 9 per cent frequency changed following the head injury to 24 per second frequency with a rather definite spiky character. Over a period of 6 minutes the record showed decreasing voltage but the frequency was sustained almost to the last; eventually only faint vertical sweeps were noted as the animal died. The

simultaneous recording of the corneal reflexes revealed a loss immediately after the trauma with return in 40 seconds. For the ensuing 90 seconds, corneal reflexes could be obtained. After that they were lost while evidences of cortical electrical activity were still present.

A different type of record is noted in Fig. 11. After blow number one, there is delta activity and during this period the eye reflexes were gone. In 2 minutes there was return of reflexes and a more normal electrical activity although some delta pattern is still present. Just after the second blow, the electrical activity of the brain did not change but its amplitude and voltage continued to decrease until a straight line record was being obtained. During part of this seeming inactivity of the cortex, the reflexes and respirations were still present to disappear again just before cessation of all activities.

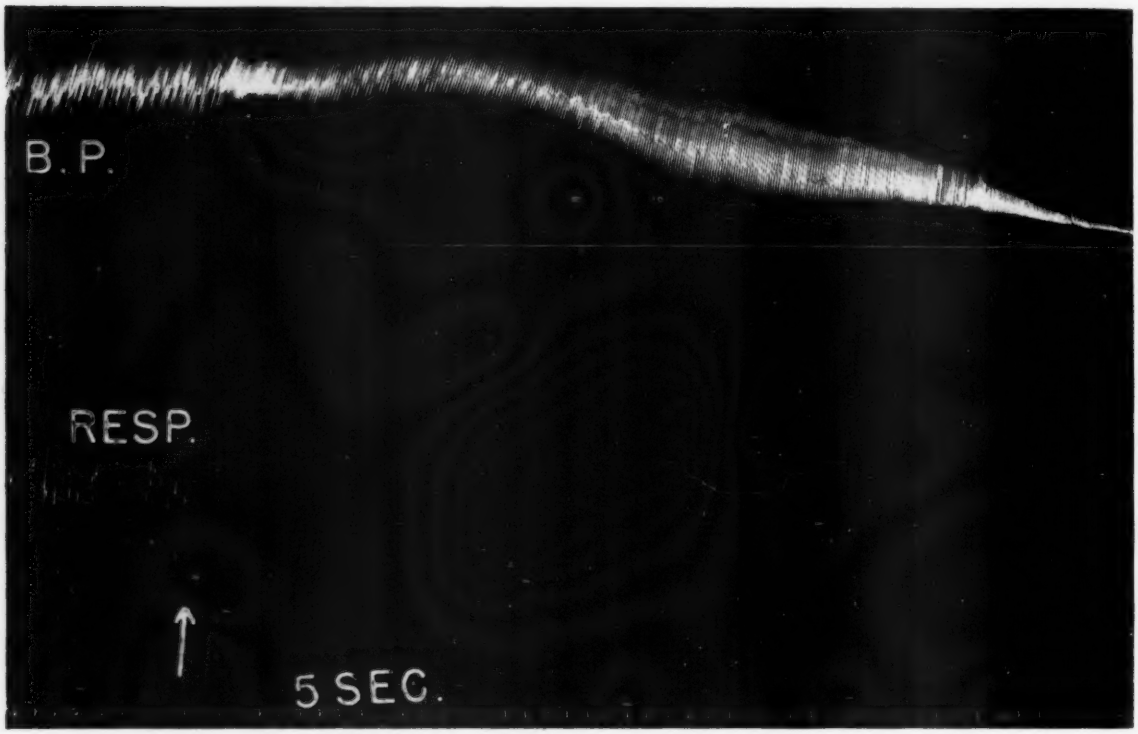

Fig. 9.—A spinal cord injury with profound effect and no rise in blood pressure. In Dog 110, a bullet wound of the spinal cord 5 cm. below the medulla resulted in rapid failure with no initial pressor effect. Apnea ensued and after 30 seconds the reflexes were lost. Examination revealed bruises and contusions of the frontal lobes. The closed-cavity hydrodynamics apparently were operative even at this low level (5 cm. below the medulla). The marked increase in the pulse pressure suggests vasoconstrictor paralysis with consequent loss of vascular-bed tone.

CONCLUSIONS

Experimental head trauma has been studied in great detail by Cannon,[1] Denny-Brown and Russell,[3] Duret,[4] Fischer,[6] Kocher,[15] Miller,[16] Polis,[17] Scott,[18] and others. For the purposes of the present discussion, the material presented by Polis in 1894 and that presented by

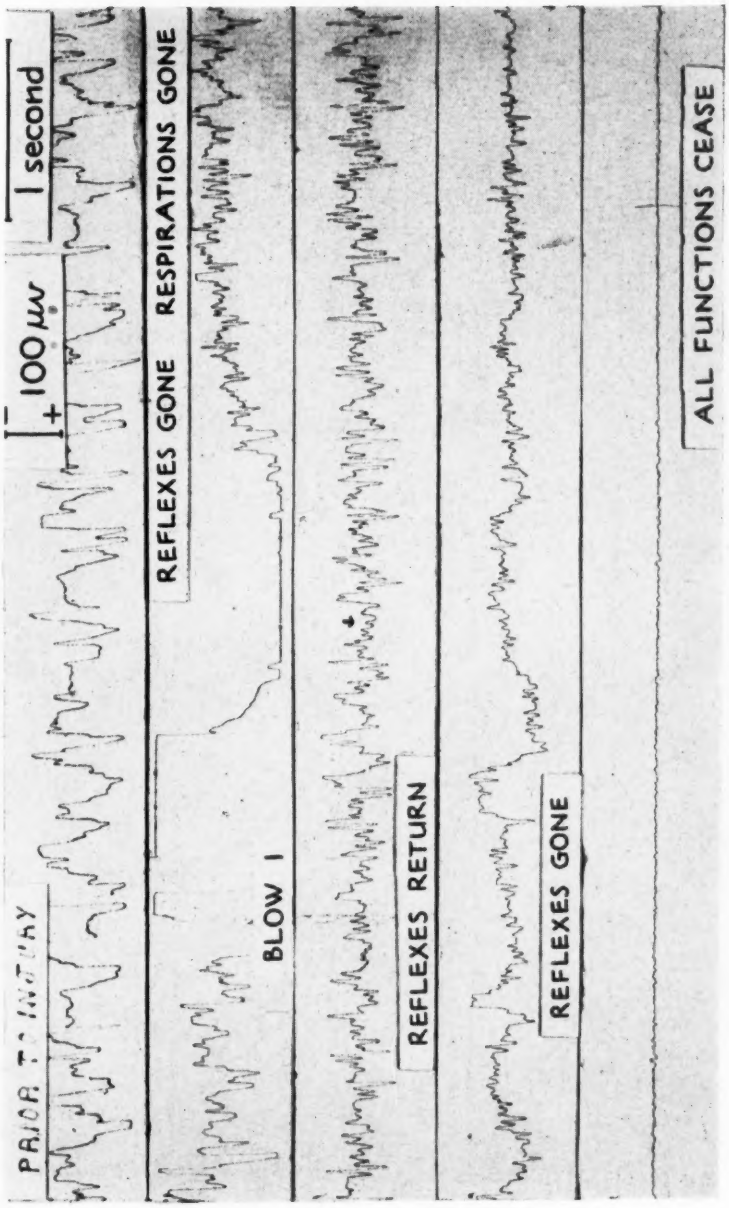
1 second
100 μv
REFLEXES GONE
RESPIRATIONS GONE
BLOW 1
REFLEXES RETURN
REFLEXES GONE
ALL FUNCTIONS CEASE

Fig. 10.

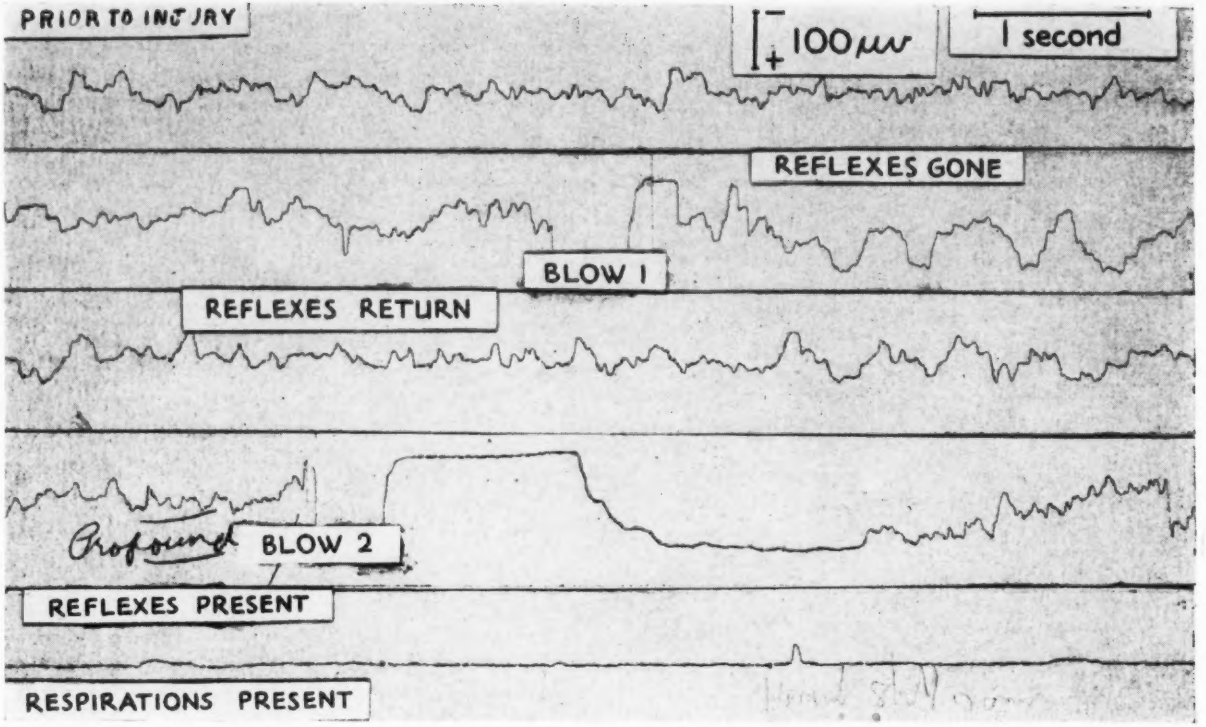
PRIOR TO INJURY
100 μv
1 second
REFLEXES GONE
BLOW 1
REFLEXES RETURN
Profound
BLOW 2
REFLEXES PRESENT
RESPIRATIONS PRESENT

Fig. 11.

Denny-Brown and Russell in 1941 are the most pertinent. The work of Polis is particularly commendable. Fifty years ago he recorded his findings in experimental head injury, including gunshot wounds, and his results with a few exceptions are acceptable at the present time. Polis worked with normal and decerebrate animals. He concluded that death from head injury results from vasomotor failure after an initial increased activity, and respiratory paralysis. He felt that in moderate injuries there was a constriction of intracranial blood vessels and that in severe injuries there was a vasodilatation. Polis described medullary paralysis without lesions, suggesting that death from concussion is through medullary paralysis. Denny-Brown and Russell have reaffirmed most of the findings of Polis. They re-emphasized the fact that in trauma to the head, medullary centers may become paralyzed with or without visible lesions in the brain stem and medulla. According to these authors, in severe trauma there is a cerebral vasodilatation, with blood pressure failure due to vagus stimulation which counteracts the pressor effect of the vasomotor center injury, eventuating in the death of the animal.

In the present study, changes in blood pressure, pulse, and respirations were carefully scrutinized in the light of associated changes in the conscious state and reflexes in dogs with morphine analgesia. Under this form of analgesia the ability to respond to painful stimulation by forceps or dynamometer was considered a sign of adequate conscious state. Lack of response to pain was seen without loss of corneal reflexes or after the reflexes had returned following an initial loss. In some animals evidences of medullary involvement coexisted with normal response to pain. Unconsciousness was always present when the corneal reflexes were lost. It was felt that involvement of the medullary ocular reflex centers by trauma represented a more severe evidence of injury than unconsciousness. The reflex of deglutition was preserved during unconsciousness but hopping reflexes were lost.

The vasomotor center was stimulated by an adequate energy, and the increase in blood pressure immediately following trauma was the most common finding in moderately and profoundly injured dogs. The exceptions to this rule were: First, when the vasomotor center was destroyed, under such circumstances there was no increase in pressure and circulatory failure occurred within a few minutes. Second, in a certain number of supratentorial blows with extensive depression of bone and laceration of brain tissue, no change or drop in pressure occurred immediately following the trauma. The mechanism of a drop in pressure following the head trauma has been described as a vagal effect by Denny-Brown and Russell,[3] and they state that such vagal effects are never seen except in subconcussive blows. In our experience, a drop in blood pressure may occur also in a seriously injured animal with eventual complete circulatory failure.

A vasoconstrictor mechanism rather than a humoral discharge causes the hypertension since adrenalectomized animals showed the usual pressor response following trauma, while the animals with section of the cervical spinal cord, and those which were adequately yohimbinized, did not. This has also been shown in Cushing[2] preparations by Freeman and Jeffers.[10] They found that sympathectomized animals did not have a pressor response on increase of the intracranial pressure by forcing saline solution into the cisterna magna. They further noted that if only the upper four thoracic sympathetic ganglia and both vagi were sectioned (denervated heart), no pressor response occurred.

In very seriously injured animals where the pressor response is followed by circulatory failure, the reason for the initial vasomotor stimulation may seem difficult to understand. Why doesn't failure occur at once? There is failure at once if the injury causes dissolution of the vasomotor center, as is shown in some of the accompanying experiments. But if the vasomotor center is allowed to remain intact, with energies acting upon it from a distance, its first discharge is, almost always, one of a peripheral vasoconstriction with consequent increase of the blood pressure. This is a protective mechanism for it helps to insure the blood supply to the brain stem and it occurs even though the vasomotor center may have been irreparably injured. The complete destruction of the neighborhood of the obex is uniformly followed by circulatory failure with no initial pressor response. In other words, a dissolution of the center itself causes the death of the animal. This is an important point. The work of Forbes and Wolff[9] has shown that stimulation of the central stump of the cut vagus causes a fall in blood pressure as well as pial vascular dilatation. It is conceivable that a depressor mechanism may be the cause of a drop in pressure in some experiments, but a paralysis of the vasomotor center itself is usually the cause of the circulatory failure and death.

While a peripheral vasoconstriction is proved beyond doubt, what is the simultaneous status of vessels in the cranial cavity? Are they constricted like the peripheral vessels? Polis[17] fifty years ago thought that in moderately injured dogs there was a constriction of intracranial blood vessels and in severely injured dogs there was a vasodilatation. Some of his conclusions were based on the bleeding time from the cut jugular vein. Denny-Brown and Russell[3] repeated these experiments. They noted the amount of bleeding from the jugular vein was definitely increased immediately after a severe trauma. They have concluded that this may represent a central vasodilatation. The work of Finesinger and Putnam,[5] Fog,[7] Forbes, Nason, and Wortman,[8] Gellhorn,[11] and others shows that the peripheral and the central blood vessels may simultaneously be in a dissimilar state of tone. With peripheral vasoconstriction due to a drop in blood pressure there is intracranial vasodilatation to insure adequate blood supply to the brain. Thus, the

presence of central vasodilatation with peripheral vasoconstriction may be the expected phenomenon and need not necessarily be construed as an evidence of traumatic stimulation of a depressor mechanism, since it may happen with any other factor causing peripheral vasoconstriction.

The evidence seems to indicate that an injury of sufficient severity to cause a paralysis of the vasoconstrictor center causes death mainly through this paralysis. The failure of the blood pressure is in fact due to the failure of the center. The stimulation of vagoglossopharyngeal centers need not be the cause of the fatal drop in blood pressure.

Respirations were affected in a multitude of ways. In the group with minor trauma usually there was no change in respirations. Occasionally stimulation associated with a slight increase in blood pressure was noted. There was apnea of varying periods in the group with moderate injuries; the respirations usually reappeared within 60 seconds. In the group with profound injuries there was respiratory paralysis with no spontaneous return in some animals or after the initial respiratory paralysis there was return for a short while with final failure and death of the animal.

Respiratory paralysis is a direct result of injury to the respiratory center. The respiratory center or the vasomotor center or both may be affected by trauma. At times the reappearance of an occasional respiratory movement has a tendency to revivify the animal with an increase in blood pressure. In the severely injured animal the vasomotor mechanism fails in spite of artificial respirations.

The pulse almost always increased following trauma. In animals with intact vagi there was an occasional vagal stimulation with bradycardia with escape from the inhibition. In one of the experiments in which the animal was decompressed bilaterally and shot with a .22 rifle, the vagal influence remained throughout, following the injury. Evidence of vagal stimulation was noted in some seriously injured dogs.

The electroencephalographic changes immediately following trauma to the head did not correlate with the medullary involvement. In some seriously injured dogs with paralysis of respirations, vasomotor mechanism, and lost corneal reflexes, the electrical activity of the brain from the parietal region continued until just before death of the animal. In others, the electrical activity of the brain failed in the presence of respirations and corneal reflexes. Obviously an injury in the neighborhood of the electrodes may be associated with cortical electrical changes transmitted through it. But in these preparations, care was taken to deliver the blow at a reasonable distance from the electrodes. Under these circumstances evidences of medullary paralysis could be obtained without a simultaneous inactivity of the brain waves.

In the human being, death soon after cranial trauma is common. In a previous report in the JOURNAL,[13] 61 of 151 consecutive autopsies were on patients dead on admission to the hospital or found dead

at the scene of the accident. In 19, there were punctate hemorrhages in the medulla and pons with little or no other associated intracranial lesions to explain the death. In this group it is very likely that death was due to medullary paralysis, and comparison of a typical pathologic picture in a fatal animal experiment with human autopsy reveals many similarities in type and distribution of lesions. (Fig. 12). Although there are no adequate human studies of clinical behavior immediately following trauma, it seems reasonable to suspect that the mechanism of death soon after injury in the human being is essentially the same as in the experimental animal.

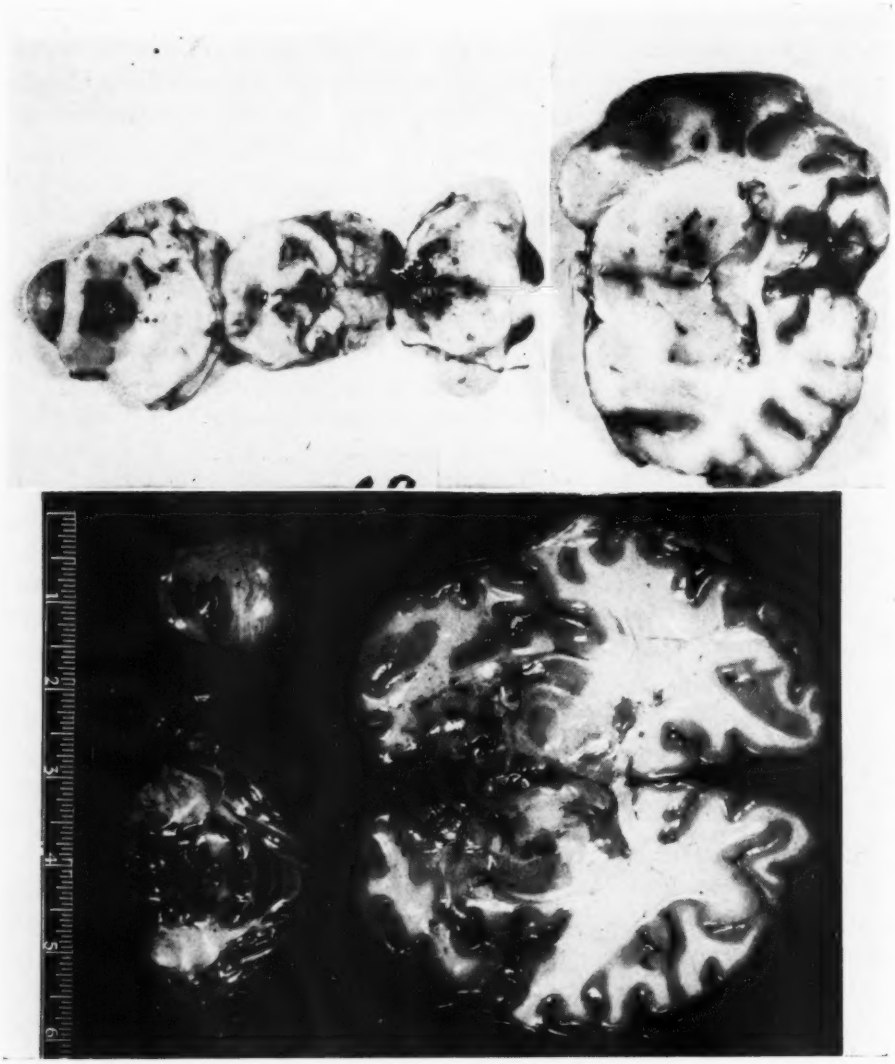

Fig. 12.—To the left, section of the brain of the dog with punctate hemorrhages in thalamus and brain stem. The animal died as a result of medullary paralysis, following a parieto-occipital head injury. To the right, section of the brain of a human being found dead at the scene of the accident. Punctate hemorrhages of the posterior thalamus and brain stem are noted. Observe the similarity of the distribution of lesions.

SUMMARY

1. The acute physiologic responses to injury may be minimal, moderate, or profound. In moderate and profound injuries usually there is a sudden increase in blood pressure with respiratory loss, unconsciousness (no reaction to painful stimuli), loss of palpebral and corneal reflexes, and frequent generalized rigidity followed by limpness. In moderate injuries the animal survived or died, in the group with profound injuries death was almost invariable.

2. Under morphine analgesia the ability to respond to pain was considered an adequate sign of consciousness. In some animals vasoconstrictor stimulation and respiratory pause coexisted with normal response to pain.

3. Loss of corneal reflexes represents a more profound response to injury than unconsciousness. Some animals were frequently observed to be unconscious with active palpebral and corneal reflexes.

4. The acute changes in blood pressure, respirations, and reflexes following trauma to the head are due to stimulation or paralysis of medullary centers.

5. The acute hypertension following trauma is caused by peripheral vasoconstriction as shown in experiments on adrenalectomized and yohimbinized animals and those in which the lower cervical spinal cord was sectioned. A drop in blood pressure following trauma was seen in some experiments. Dissolution of the vasomotor center by .22 rifle caused failure without an initial pressor response.

6. Respiratory paralysis is a common manifestation in severely injured dogs. However, in some with pressor response there was little or no change in respirations and in others with respiratory paralysis there was little or no change in vasomotor activity. Increase in respiratory rhythm associated with other evidences of medullary stimulation was possible but infrequent.

7. Evidences of vagal paralysis were common in most of the moderately and severely injured animals. Vagal stimulation with bradycardia was seen in some moderately and severely injured dogs.

8. The depressor centers mediated through the vagoglossopharyngeal complex may have been stimulated to cause a drop in blood pressure in some experiments but it is felt that the vasomotor failure is mainly due to a failure of the vasomotor center in the medulla.

9. Electroencephalographic studies of the cortex with simultaneously observed evidences of medullary paralysis reveal that the cortical activity may be unhampered even though the medulla is badly damaged and vice versa.

10. In the experimental animal, death from acute trauma was due to paralysis of the vasomotor center.

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THE EFFECT OF POSITION ON SHOCK PRODUCED BY HEMORRHAGE

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ACCUMULATED experimental evidence forms a concrete basis for our present conception of many of the changes occurring in shock, from whatever cause. Thus, most of the measures used clinically in the prevention and treatment of shock have an accepted physiologic basis. The so-called shock position is probably an exception to this rule, for although elevation of the foot of the bed seems to be universally regarded as the proper position for the patient in shock (provided, of course, that chest or head injuries do not exist), there is, as far as I am aware, no experimental evidence to support such a maneuver.

METHOD

Medium-sized mongrel dogs weighing 6 to 12 kg. were used as experimental animals. They were allowed to have water but no food for a period of eighteen hours prior to the experiment. Each animal was tied flat on its back on an animal board; the boards were then tilted so that one group of dogs had the head raised with the long axis of the body 30 degrees from the horizontal, while the other had the head lowered to a similar degree, and this position was maintained for the duration of the experiment. Thirty-two dogs were used, sixteen in each of the designated positions. Two or four dogs were bled at a time, and an effort was made to use animals as much alike in weight and general characteristics as possible on each occasion. Alternate animals were placed in the head-up and head-down position, as described.

The femoral artery was cannulated without the use of general anesthesia and a certain amount of blood was removed at hourly intervals. On each of the first three bleedings, an equivalent to 1 per cent of the body weight of the animal was removed; following this, ½ of 1 per cent of the body weight was withdrawn each hour, until the animal died. (This fractional method of bleeding was found to be more satisfactory for our purpose than any of several other methods tried.) Blood pressure and, in some instances, hematocrit determinations were made immediately after each bleeding, and the general condition of the animals was frequently observed. The total amount of hemorrhage before death was measured, and survival times were carefully noted. There was no replacement therapy. The temperature of the room in which the experiment was conducted was usually constant at 25° C., but varied on occasion between limits of 23 and 27° C.

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RESULTS

Fig. 1 shows the average amount of hemorrhage before death and the average survival times for each of the two groups of sixteen dogs used. On first examination, the figures might be interpreted to indicate a greater difference in the survival time of the two groups than in the amount of hemorrhage. This, however, is not the case, but is due to the smaller amount of blood withdrawn each hour in the latter part of the

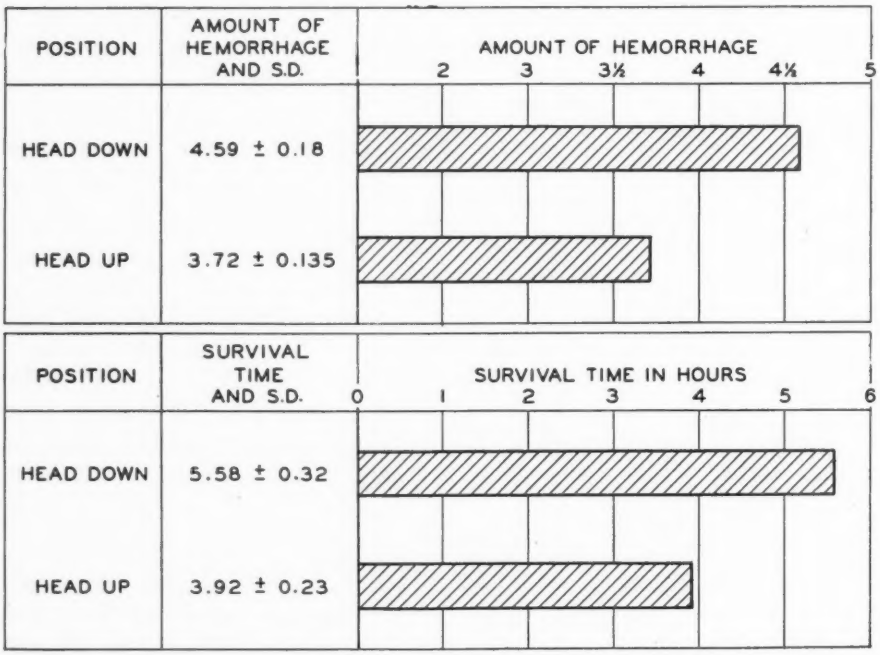

Fig. 1.—Mean amount of hemorrhage producing death, and survival times, for each of the two groups of dogs used in the experiment. Each figure represents the average amount of hemorrhage before death, or the average survival time for the sixteen animals in that particular group, with *S.D.* the standard deviation of the mean as calculated from statistical formulas. Amount of hemorrhage is expressed as percentage of body weight; survival time is given in hours.

experiment, as shown in the illustration. Average systolic blood pressure determinations for the two groups during the course of the experiment are given in Fig. 2, while Fig. 3 shows the average hematocrit figures for sixteen of the animals, eight from each group. It must further be noted that in general the animals with the head up seemed to remain alert and active until near the end, with death supervening suddenly, whereas those with the head down were quieter, became gradually less alert, and frequently were comatose for some little time before death.

DISCUSSION

The difference between the mean amount of hemorrhage resulting in death for the animals with the head up and for those with the head down amounts to 19 per cent of the larger value. That this is of real

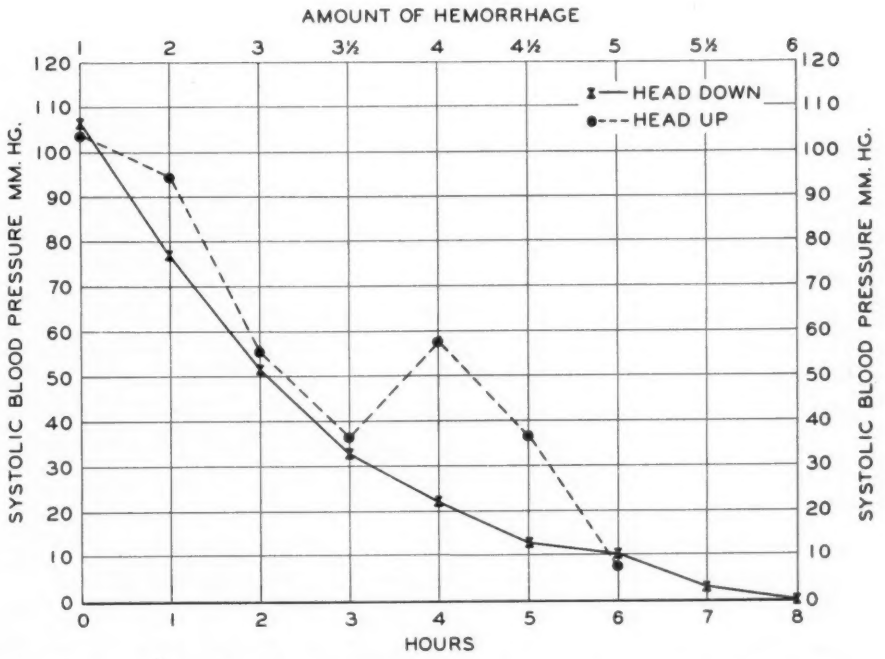

Fig. 2.—Average hourly systolic blood pressure readings for each of the two groups of sixteen animals.

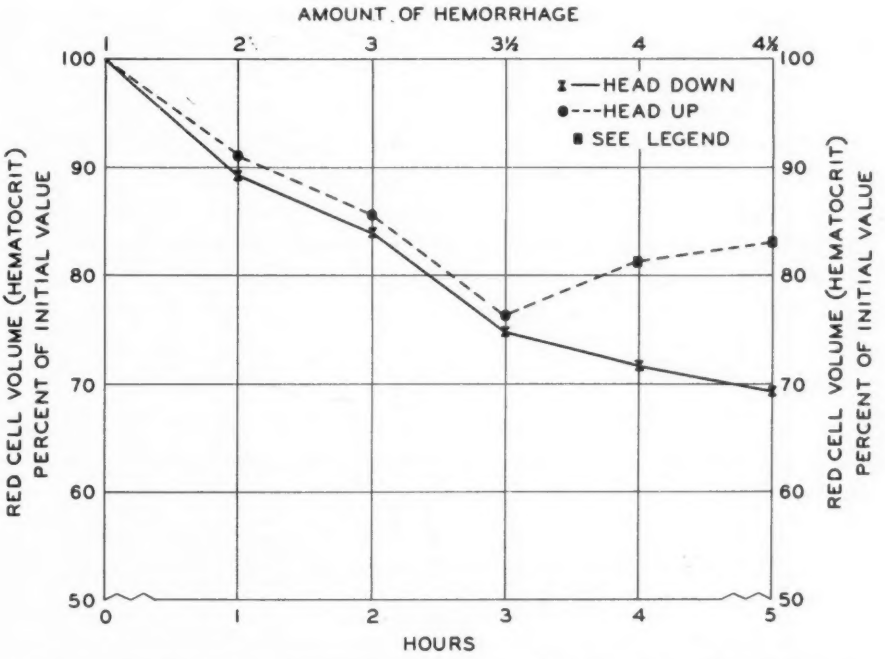

Fig. 3.—Average hourly hematocrit readings for each of two groups of eight dogs. The average initial values are represented as 100 per cent, and the following readings are given as percentages of the initial value. The last two values on the broken curve marked " ■ " are averages for four and three animals in the head-up group remaining alive at these respective times, and are not true representatives of the average of the whole group.

statistical significance is indicated by the standard deviations, as given in Fig. 1. Thus, it seems quite clear that dogs placed so that the head is elevated 30 degrees will survive some 20 per cent less fractional hemorrhage than will those placed with the head down 30 degrees. All environmental factors such as temperature are controlled by the performance of the experiment on the two groups under identical conditions. Therefore, it may be stated with some certainty that, within the limits of the experiment performed, lowering the head of the animal is beneficial in the treatment of shock produced by repeated hemorrhage at hourly intervals. It is true that the supine position is unnatural for a quadruped such as the dog, so that great caution must be exercised in attempting any clinical implications. It is known, however, that the blood pressure regulating mechanism for posture in dogs is similar to that in man, with adequate compensation occurring for postural changes of relatively short duration. Since the experiment herein reported was of an acute nature, lasting not longer than eight hours, it seems reasonable that the cardiovascular system of the dog may behave in a similar fashion to that of the human being under like circumstances.

No new light is afforded to explain the beneficial effect of the shock or head-down position by this experiment, but our results are consistent with the commonly held view that blood flow through the vital centers is maintained more adequately by lowering the head. The smooth blood pressure decline and gradual collapse of the animals with the head down, compared to the irregular blood pressure changes and more sudden death of those with the head up, suggests less uniform action of the integrated compensatory mechanisms involved, in the latter group.

The hematocrit determinations are probably not of much significance. The greater and more uniform decline of blood pressure in the head-down group would tend, by lowering capillary pressure, to promote the passage of fluid from the tissues into the vascular system, thus helping to produce the steadier decline in the hematocrit value already noticed, compared to the higher blood pressure and less hemodilution in the other group.

CONCLUSION

In the dog, shock produced by repeated small hemorrhages is beneficially influenced by the head down, Trendelenburg, or shock position. These findings may have some clinical significance; if they do, confirmation of the standard procedure of raising the foot of the bed in the treatment of shock is presented.

SPOOL COTTON AS SUTURE MATERIAL

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SPOOL cotton was the only suture material used in 1,659 general surgical procedures. Our results are reported to lend emphasis to the observations of other workers and to stress certain advantages not generally appreciated which we believe accrue with the use of cotton. Our observation of these cases has caused us to view with enthusiasm the use of cotton sutures in most general surgery. The definite clinical advantages of wounds healing with minimal cellular reaction have been reported without stressing the surgical advantages which ensue with the use of cotton. We believe that these advantages become apparent with consideration of this fairly extensive series of cases.

Ordinarily, nonabsorbable sutures have been considered by many surgeons to be the only ones possessing "foreign body danger." Fear of this impels many to avoid the use of nonabsorbable sutures. Strain[1] emphasized the important fact that, absorbable or not, any suture is a foreign body. However, it is essential to realize that foreign bodies vary in the degree of local tissue reaction and that the absorption of absorbable suture induces much more tissue reaction than does the mere presence of nonabsorbable suture. We believe that the decreased tissue reaction of cotton far outweighs the "foreign body danger."

Meade and Long[2] have shown cotton to possess the desirable qualities of pliability, adequate tensile strength, a high coefficient of friction, and stability on exposure to heat and moisture. Meade and Ochsner's[3] investigation showed that cotton produced less cellular reaction than silk, linen, or catgut. Cotton is inexpensive, easily obtained, and readily transported. Special sterilization procedures are unnecessary providing care is taken to avoid fracture of the fibrils. This is readily accomplished by winding the cotton loosely on collapsible material such as rubber tubing.

The observations of these workers have been generally substantiated by others who have had considerable experience with cotton, and for this reason we had little hesitancy in adopting cotton for routine use as a suture material. Without exception, we have found that three sizes of spool cotton are adequate for general surgery. Size No. 60 is used for ligature of small vessels and occasionally for suturing wounds where the cosmetic result is important. Size No. 40 is used routinely for the closure of peritoneum, suture of bowel, stomach, muscle, subcutaneous tissue, and skin. Size No. 20 is used for the suture of

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heavy fascia and the ligature of larger vessels and ducts. Stay sutures have never been considered necessary with cotton. Ordinarily, the peritoneum and skin are closed with a continuous stitch and all other sutures are interrupted. Care is taken to tie square knots and sutures are cut short. Cotton is finer than catgut and is technically more difficult to use. We believe this increases the surgeon's dexterity and meticulousness.

In one case of a recurrent inguinal hernia which we reoperated upon after nine months, the cotton sutures used in the first operation were difficult to find. There was but little fibrosis along the suture line in the external oblique fascia. The microscopic report showed mild fibrosis with minimal foreign body reaction about the suture. In all our experience we have seen no case of sensitivity or any unusual tissue reaction to cotton.

In this series of cases cotton was buried in every case and was the only suture material used. The postoperative wound complications were divided into two groups, a stitch abscess and a more severe infection. Of the 1,659 cases, 281 wounds were contaminated and 1,378 were clean. Of those contaminated, 11.4 per cent developed stitch abscesses and 3.6 per cent developed severe infections. Of the clean wounds, 2.1 per cent developed stitch abscesses and .5 per cent developed severe infections. Reference can be made to Table I to see the distribution of these complications.

At this point, it should be emphasized that only about two-thirds of all contaminated wounds at the hospital were closed primarily. Ordinarily, any wound with contamination over six hours old, regardless of how clean it might look, was left open, and in all which were closed primarily, a meticulous débridement was done. Sulfanilamide crystals were used locally in all contaminated wounds and, in addition, many patients received the drug orally.

All members of the surgical staff have been impressed by the fact that these wounds, clean or contaminated, showed much less induration, edema, and tenderness than we encountered in our work in civilian life, where almost without exception, catgut was the suture employed. The scars are soft and pliable and there is no distressing deep tissue induration which constantly reminds the patient of his incision. This fact is important from a military viewpoint, because we are convinced that the soldier pays less attention to his scar; and accordingly, the number of patients developing hypochondriacal ideas in reference to scars has been small. We have had three patients who have returned to the hospital complaining of pain in the incisional site to such an extent that they were unable to perform their duties. All three patients had other complaints which were not substantiated by the presenting pathology, and those patients were ultimately disposed of by the neuropsychiatric service.

TABLE I

DISTRIBUTION OF COMPLICATIONS

TYPE OF CASE	NO.	MINOR INFECTION	SEVERE INFECTION
Amputations			
Clean	3		
Contaminated	21	3	1
Appendicitis			
Acute	297	6	
Chronic	48	2	
Normal	19		1
Ruptured	27	2	4
Arthrotomies			
Clean	17		
Contaminated	3		1
Bone tumors	25		
Cholecystectomies	5		
Cysts and subcutaneous tumors	320	9	2
Foreign bodies			
Clean	5		
Contaminated	9	2	
Hernias			
Inguinal	282	4	2
Incisional	14		
Of muscle	17		
Epigastric	16	1	
Femoral	12		
Hydrocele	35		
Intestinal obstruction			
Acute	5		
Mastectomies	16	1	1
Perforated peptic ulcer	4		
Tenorrhaphies			
Contaminated	41	3	2
Thyroidectomies	4		
Varicose veins	214	6	1
Varicocele	24		
Wounds			
All contaminated	176	22	2
Total	1,659	61 (3.7% of total)	17 (1% of total)

As a routine part of the repair of inguinal hernias, the external and internal rings can be closed more snugly than was possible with catgut. This seems to be explained by the fact that the swelling produced by cotton is less and thus the rings can be more tightly closed without compressing the cord. Routine support of the testicle and cord is not necessary to prevent edema and discomfort.

Of our total of 341 hernias of all kinds, we have had four recurrences that we have been able to find. Two of these were femoral, which were operated upon through the subinguinal approach, and at the second operation an inguinal approach was made and neither recurred. Two inguinal hernias recurred and one was reoperated upon with a successful result; the other patient was separated from the service. To our knowledge, none of our laparotomy patients has developed an incisional hernia. We operated upon fourteen incisional hernias and fifteen recurrent inguinal hernias with no recurrences. One recurrent hernia had been operated upon three times, the fascia

lata being used twice. There was no recurrence after the fourth repair, and the patient was returned to full combat duty.

One patient with a bilateral hernia developed an acute bronchitis on the third postoperative day, and a bilateral pneumonitis on the seventh postoperative day. He coughed severely for seven days, but by the twenty-first postoperative day had made an uneventful recovery and four months later there was no recurrence of the hernia.

One patient with bilateral inguinal hernia developed a septic temperature on the fourth postoperative day with a fluctuant mass in the left incision. The skin sutures were removed and about 30 c.c. of thick creamy pus were evacuated and the wound was drained. The cotton sutures in the external oblique fascia remained in place and the wound healed without sinus formation and with no recurrence of the hernia. We have not observed in cotton the tendency toward sinus formation that exists in silk and chromic catgut.

One patient with a bilateral hernia developed a massive unilateral atelectasis with a severe cough. Bronchoscopy was used and 250 c.c. of mucus were removed by suction. A mild bronchopneumonia followed with complete recovery in three weeks. There was no complication of the wound and no recurrence of the hernia ninety days postoperatively.

It should be emphasized that all of the patients in this series were young men in excellent physical condition and were physically superior to the average civilian patient.

CONCLUSION

1. Spool cotton is an excellent suture material for all types of general surgery, including clean and contaminated wounds.
2. It is technically more difficult to handle than catgut and is thus conducive to meticulous surgery.
3. It possesses minimal "foreign body danger."
4. Induration, serum accumulation, and postoperative wound infections are minimal with cotton.

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COTTON SURGICAL SUTURE MATERIAL

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MANY surgeons are now using cotton thread as their routine suture material instead of surgical gut.[1] Other types of nonabsorbable suture material are becoming popular also, but evidence of the superiority of cotton has been rapidly accumulating in the past few years.[2] We expect that a full appreciation of the virtues of cotton will result in its wide adoption, with absorbable and other suture materials being used only where their particular qualities are specifically indicated.

We must avoid the mistake of learning again, now at our patients' expense, facts which were proved years ago. Nonabsorbable suture material was given a trial and rejected by the rank and file of surgeons fifty years ago when catgut first became available. The plebeian cotton thread was not given a serious trial then; it is very possible that if it had been, the course of surgical history would have been different.[3] The aristocrats of threads, silk and linen, were tried instead, but too often wounds repaired with them would become infected and drain for months until the sutures were extruded or removed. This seemed natural because after all the suture was a very foreign body. These draining sinuses were very embarrassing to the surgeon. Halsted, however, demonstrated that with careful technique fine silk sutures could be used which did not necessarily extrude with infection.[4] Few surgeons attained such perfection and even an occasional draining sinus was sufficiently discouraging to any surgeon in private practice. Catgut then was welcomed as a means of avoiding such embarrassment.[5] A superficial consideration accepted it as a more natural suture material. Of course, the surgical wounds became infected even more often and then the catgut might be extruded. The wounds were often painfully indurated, and occasionally disrupted entirely. These complications usually occurred promptly, however, and were not so obviously the fault of either the surgeon or the catgut.

The fact is that surgical gut can only be described as a very irritating substance to place in a surgical wound, the new fine sizes and recent improvements of manufacture notwithstanding.[6] It is irritating because of the large bulk necessary to hold the wound together and because of its chemical and biological constitution. In some patients the inflammatory reaction is so violent as to suggest an allergic reaction. Its only virtue is its transiency and the very process of absorption of it is deleterious to wound healing. Surgeons who have kept accurate records have reported infections in from 4 to 11 per cent of clean wounds when surgical gut is used.[7-9] Such wound infections are less than one-third

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as frequent when cotton suture material is used.[10] Not only do fewer clean wounds become infected but many grossly contaminated wounds will gratifyingly and surprisingly heal cleanly.[11] Every operative wound is more or less contaminated, of course. The germs fall into it from the air, or in droplets from the respiratory passages. There may be breaks in the aseptic technique or they may enter the wound during transient bacteriemias, which are more frequent than is usually appreciated. If the resistance of the wound has been impaired by trauma or by the presence of irritants such as surgical gut, infection commonly follows.

Other suture materials have been proposed. Isografts of fascia lata or cutis are possibly the least irritating of all but have obvious limitations. Various metal wires are well tolerated by the tissues chemically but are awkward to handle, radiopaque, more apt to cut through, and mechanically irritating by their stiffness. Silver wire was tried and abandoned too, years ago. Linen thread is the most irritating of the ordinary threads. Nylon is a generic name for synthetic chain-forming polymeric amides of a proteinlike chemical structure. There are literally hundreds of such substances possible. The thread we have tested has been supplied for surgical use and also some was purchased in a variety store. It has been well tolerated by the tissues but is very elastic and the knots are not dependable. Dermatitis from nylon hose is common enough to arouse suspicion of its irritating qualities.

Silk has been the most widely used and intensively studied of the various nonabsorbable suture materials.[12, 13] It is only mildly irritating chemically. Being essentially a straight fiber when it is spun or woven into thread, microscopic open dead spaces occur which harbor infection and are the mechanism causing the persisting draining sinuses. The minute stiff straight ends stick out from the main strand. As commercially supplied to the surgeon it is usually heavily impregnated with a paraffin wax. In spite of its disadvantages it has been earnestly advocated by very successful surgeons and Cutler has said that the occasional draining sinus is a small price to pay for the firmer healthier healing of the wounds.[14]

Cotton possesses all the virtues of silk without its disadvantages. It can be used in infected wounds without fear of its being extruded through chronically draining sinuses, provided it is properly placed. Its naturally curly fibers twist to form a compact thread.[15] Possibly because it is a vegetable carbohydrate rather than an animal protein it is not as irritating chemically. Placing short lengths of suture materials in the anterior chamber of the rabbit's eye has visibly demonstrated the minimal reaction of cotton.[16] Waxing is not necessary nor desirable. Size for size, dry, it is slightly weaker than silk but when wet it gains strength whereas silk loses strength. When in place in the tissues the cotton is as strong as silk. It retains its strength much better and does not swell. Regardless of the theoretical explanations or reasons, the

observed and demonstrated facts are that wounds repaired with cotton suture heal with maximal strength, speed, and comfort, and with minimal inflammation, infections, disruptions, and other complications.[17]

Cotton thread has been used extensively in commerce for many years and the best possible thread should already exist. However, the objective of the sewing trade has been a strong thread to be sure, but also a slippery thread which would slide easily through the cloth and the eye of a sewing needle. Moreover, if greater strength were necessary a slight increase in bulk was not so objectionable. The slipperiness has been obtained by singeing the loose ends off the thread in a gas flame and then adding wax or starch. An alizarin blue dye is commonly used to increase the whiteness and some soap may be left in the thread after the bleaching process. Mercerizing also produces a slippery thread with a high luster. Mercerizing is done by soaking the thread briefly in a strong caustic soda solution. This shrinks the thread and increases its strength although only in proportion to the swelling and increase in cross sectional area. The thread is kept under tension so it does not swell and shrink too much. The chemical nature of the thread is not changed but a different crystalline structure is induced and the thread is more absorptive.

The surgeon's problem is to find the strongest possible thread for size when tested knotted and wet and without the addition of irritating substances like starch, wax, dyes, soaps, etc. When cotton thread breaks, only about one-fourth of the fibers break and the rest of the fibers pull out. The advantage of a long fiber and a tight twist can readily be appreciated. The longest fiber is found in sea-island cotton (*Gossypium barbadense*) which is grown best under the climatic conditions found on the islands off the coast of the Carolinas and Georgia. This long staple cotton almost ceased to be available several years ago due to the ravages of the boll weevil. It is staging a comeback but only a very small amount is available. Its fibers range up to two and three-eighths inches long. The fibers of irrigated desert (Egyptian) cotton from Arizona, of which most thread is made, are about one and one-fourth inches in length. The ideal surgical suture cotton thread will some day be made out of long fiber Sea Island cotton meticulously carded to remove the short fibers, thorougly bleached and washed to remove all impurities and natural oils, especially spun with an as yet undetermined twist to produce a maximum strength when knotted and wet, without kinking, and without the addition of any dye, starch, wax, or other filler. Such a suture of pure cotton fiber will approach the chemical innocuousness of tantalum wire and still be soft and stronger than any thread now available. Since no such thread is now available, for most of our work we have purchased ordinary plain white housewife's spool cotton sewing thread (Clark's O.N.T.) at a variety store. We have not been particularly dissatisfied with it except for the natural

desire for the best possible. This is a six-cord thread of good strength and containing very little extraneous substance. Technically it is a quilting thread although of soft finish. Most so-called quilting cottons are of a *glacé* finish impregnated with starch or wax. Although the full physiologic effect of mercerizing and the addition of dyes, starch, etc., has not been fully determined experimentally, and they are evidently not too irritating, they are at best unnecessary complicating factors. We have found slightly stronger threads but they were all contaminated with fillers and we have not felt that the slight additional strength jusified their use.

We take advantage of the cheapness of cotton thread to facilitate its use. Its cost per operation is less than 2 per cent of that of silk or surgical gut. Cheapness is the least of its virtues, however; the operating table is no place for economy but rather that the best is none too good. We prepare it in skeins of thirty strands. The thread is wound thirty times around a wooden board cut with steps six, seven and one-half, and nine inches long. We use Size 60 in twelve-inch lengths as being the most convenient length for the one-handed tie. Size 40 is prepared in fifteen-inch lengths as a slightly longer strand allows the clamps on the ends of each stitch to hang further away from the incision. Larger sizes are prepared in eighteen-inch lengths. The various lengths serve to distinguish the various sizes although one soon becomes familiar with them. At one end of the board the bundle of thread is rubbed with paraffin and held momentarily against a hot sterilizer or autoclave. This melts the paraffin, which soaks into the thread. The bundle is then cut with a razor blade through the center of the paraffined area. This provides paraffin-stiffened ends to each strand which facilitates threading the needles. In use it works out that the paraffined ends are never left in the wound although it probably would not matter much if an occasional one was. The skein of thread is tied with a single strand at the middle and near each end so that the threads can be pulled out from the ends without snarling. The skein is coiled loosely on itself and tucked into a pocket of a prepared muslin envelope for sterilizing. These envelopes are made with four pockets for three sizes and a long strand of the skein. Additional supplies of various size threads are kept sterile in jars in the operating room. The thread is autoclaved although it can be boiled and used wet.[19] It is only sterilized once although it does not lose much strength on repeated autoclaving. It shrinks temporarily during sterilization and must not be wound on rigid spools.

Certain principles of surgical technique must be practiced when non-absorbable suture material is used. Mistakes such as improperly placed sutures which are only temporary as when held with surgical gut are eventually adjusted by the healing process. When errors of technique are perpetuated by permanent suture material they may have to be rectified subsequently by surgical removal of the strand. Gentleness in the

handling of tissue and accurate dissection are important regardless of the suture material used. One reward of carefulness is a reduced incidence of perforated gloves, one or more of which is perforated in at least 50 per cent of operations.[18] Vessels should be grasped with small pointed clamps. Ligatures should be placed upon just the vessel, avoiding the strangulation of large tags of tissue in the ties. A transfixing suture is often the best tie. Suture lines should be sewed with the smallest effective size of suture material and with the smallest effective bit of tissue in each stitch. Small needles with taper points are desirable, such as Mayo No. 6, Ferguson No. 10 or 12, and Kelly Intestinal No. 4. Tissues are to be opposed without dead spaces but also without squeezing else the sutures will cut through. Nowhere should a portion of the suture strand bridge across as a chord subtends an arc creating a dead space in which serum can collect. Continuous suture is less desirable than interrupted stitches if the latter are placed with uniform tension. This can be accomplished only by placing all the stitches in any one row before tying any of them. The wound is then held together by the assistant by traction of the untied strands so that beginning at one end of the incision each stitch can be tied in succession without tension. Wounds must be dry on closure and when drains are necessary they should exit through a separate stab wound and not through the suture line.

We have used cotton thread mostly in No. 40 for sutures and No. 60 for ligatures. No. 80 has been used for tendon suture and No. 100 for nerve suture. If tissues are sutured with more tension than No. 40 will hold, the stitch will probably cut through anyway. The exception to this is the upper abdomen where the stress of postoperative vomiting may require a stronger thread such as No. 20, or the wound may be reinforced with snugly tied stay sutures of No. 10. Beginners first adopting cotton should use larger sizes unless they have already had considerable experience with fine silk. Doubled strands should never be used. Experimental wounds contaminated with staphylococcus extruded the stitches only when the cotton thread was used double. The figure-of-eight stitch is undesirable because of the doubling at the crossing of the strands; their pully action is unnecessary because wounds are held closed during the tying. Mattress stitches are frequently used, however. The tendency is to demand a larger thread for easier tying without regard for the requirements of the wound. The fine sizes are usually as strong as the tissues. Thirty or more needles are used and already threaded before the operation is begun. Each strand is used for but a single stitch or tie. The one-handed knot is almost essential since it gives substance to the delicate strands by keeping them under tension. Knots hold very well especially when wet, but are not infallible. We commonly use triple-throw knots and are careful to tie them square. This is very quickly done and almost automatic with the one-handed knot. With the fine sizes the knots are minutely small anyway. The ends are cut on

the knot less than 1 mm. long. The residual ends sometimes stick to the gloves and are troublesome to get rid of. They are more easily discarded if they are of some length. When the cotton thread is used dry and the knot pulled too tight the strand usually breaks in the dry part some little distance from the wet bloody knot. This leaves a short wet end near the knot of sufficient length to finish the knot with the use of artery forceps. We commonly use a continuous stitch for the skin as interrupted skin stitches seem unnecessarily meticulous. There is just enough "hang" to the cotton strand through the skin that the traction of an assistant on the skin stitch is unnecessary. Cotton thread pulls out very easily, and is quite painlessly removed from the skin and when used for deep stay sutures. It is superlative as a subcutaneous stitch for meticulous closures on the face because the strands easily pull out long distances if left in eight or ten days.

It is not to be denied that surgical gut and other suture materials are of value. Especially is this true of fascia lata in the repair of hernias.[20, 21] Wire will occasionally be desirable for its tensile strength as in bone work. Silkworm gut is still acceptable for stay sutures which traverse the entire abdominal wall. To change from surgical gut to cotton usually adds about 30 per cent to the operating time although this differential can be reduced by teamwork and skill.[22] Any prolongation of the operating time may not be justified in certain emergency operations, such as splenectomy for ruptured spleen, but hurry is the least valid excuse for poor surgical technique.[23] Anywhere that a continuous suture is very desirable, such as the gall bladder bed after cholecystectomy or the vaginal stump after hysterectomy, surgical gut should probably be used for suturing although we have used continuous cotton thread successfully for the serosal stitch of enteroanastomosis and (experimentally) in abdominal closures. Instances where very large bites of tissue are necessary, such as perineorrhaphy, may require surgical gut.[24] The intestinal mucosa tolerates poorly a continuous nonabsorbable suture, and hemorrhoidectomies are preferably sutured with surgical gut. The urinary tract mucosa should not be sutured with permanent suture material. There is no inherent antagonism between surgical gut and cotton; one merely sacrifices the advantages of cotton with the use of the gut. There is probably no instance where silk is preferable to cotton.

The essential question is: can one use cotton or any nonabsorbable suture material in surgical wounds without risking the embarrassment of draining sinuses and having to remove each stitch later? The word embarrassment is used advisedly because usually the wounds heal firmly without hernia even with the sinuses.[25] It has been just this embarrassment which has precluded the universal acceptance of silk. Evidence is accumulating that when cotton is properly used it can indeed be used without fear of such embarrassing sinus formation. This does not mean

that in the profuse drainage of a severely infected wound there may not appear an occasional sloughed out cotton suture or ligature, but when the acute infection subsides no cotton suture in the depths of the wound will constitute a foreign body to preclude healing.[26] We have used cotton in infected wounds such as pilonidal cysts and in contaminated wounds as after appendectomy which occasionally became infected later, and have yet to remove an offending cotton stitch.[27] On the other hand we have removed many silk stitches and catgut strands. We have observed that healing infected wounds invariably granulate in, and cover without delay, buried cotton ligatures. We have been impressed with the rarity of infection in wounds repaired with cotton in patients whose appendix had ruptured or was gangrenous. This improvement may have been in part due to the benefits of sulfanilamide. We have admired the minimal inflammatory reaction in wounds repaired with cotton. Possibly the most convincing evidence of all is that we have observed reluctant surgeons habituated to surgical gut become enthusiastic over the superiority of cotton by observation of the results obtained.

Comfort is difficult to evaluate but one woman who had a low midline wound repaired with surgical gut, and seventeen days later a long right rectus incision repaired with cotton, voluntarily testified to the markedly less discomfort from the latter wound. This patient also had a single cotton stitch work up to the surface of the wound in the seventh week. No discomfort was associated with the event; in fact, she did not think enough of it to call or show it to her surgeon. A skin incision in the thigh for fascia lata had three small serum pockets appear in the eighth and ninth week which were punctured and drained for a few days. These resembled the common sequelae to the use of surgical gut. No fragments of cotton thread could be identified in the drainage and the wounds closed promptly. These two episodes have been the only late complications (if they can be called such) we have observed in an experience of using cotton for more than a year.[28]

There is an old adage that "Never is never true." We cannot say that cotton suture material will never cause a persistent discharging sinus until its strands are extruded, but we do believe the possibility of such an embarrassment to be so remote that we use cotton now when we were unwilling to use silk formerly. The implications of this fact are not readily appreciated but it is plain that potentially infected wounds particularly should be afforded the advantages of cotton suture. Surgical gut is least reliable and most unsatisfactory in the presence of infection. It does not survive to hold the wound together and serves as a culture medium for the invading organisms. Silk has been used in the presence of infection only with misgivings that each stitch would later have to be retrieved. Cotton sutures can be used without this fear but with assurance that they will hold the wound together throughout the infection and not deter healing after the infection subsides. Any in-

fection will not be aggravated and the incidence of postoperative hernia minimized. Of course, good surgical judgment often precludes any suturing of an infected wound either with cotton or anything else.

It is unfortunate that in order to introduce a new surgical technique or procedure it is necessary to seem to derogate the formerly acceptable practice. Mental inertia provokes argumentative extremes but the problem is to maintain an intelligent perspective. Excellent surgeons have accomplished surgical miracles with surgical gut. Some surgeons have become enthusiastic about silk and other suture materials. Enthusiasm does not justify the exclusive use of any one suture material. At present cotton thread appears to possess virtues justifying the preference position. It introduces significant new considerations into the old controversy between absorbable and nonabsorbable suture material. Perhaps in time an even better suture material will appear. We confidently expect a better cotton thread to become available. The earnest surgeon need not be the first to adopt the new but neither should he be the last to abandon the old. Even if the new method requires the acquisition of new skills this should not be allowed to be an obstacle. The one-handed knot and familiarity with the delicate strands can be acquired in large part by practice in the privacy of one's own study. An anesthetized patient should not be kept waiting while his surgeon amateurishly attempts to learn procedures requiring special skill.

CONCLUSIONS

1. Plain cotton thread is recommended as the suture material of choice for routine use.

2. If properly used there is no danger of draining sinuses and extrusion of the stitches.

3. It is especially desirable for the repair of contaminated wounds.

4. Surgical gut, fascia lata, and wire are valuable for certain purposes.

5. Silk has no clinical advantages over cotton and should be replaced entirely by cotton.

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SURVIVAL OF RHESUS MONKEY FOUR YEARS AFTER EXCISION OF HEAD OF PANCREAS WITH OCCLUSION OF EXTERNAL PANCREATIC SECRETION

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SINCE it has now been repeatedly demonstrated that resection of the entire duodenum and head of the pancreas with occlusion of external pancreatic secretion is feasible in man with immediate survival in good condition, the question is raised of the possibility of indefinite survival under these conditions.

Excision of the head of the pancreas with ligation of the neck was carried out in Rhesus monkeys and the observations reported elsewhere.* The body and tail of the pancreas distal to the ligature were converted into an elongated cystic structure not more than 1 cm. in diameter and of approximate length of the original organ, as a result of dilatation of the main pancreatic duct. There was complete atrophy of acinar tissue, and numerous rather large islets persisted in the cyst wall.

One of the monkeys survived for four years. Its history follows.

Male *Macaca rhesus* of unknown age. In March, 1940, laparotomy was performed and the head of the pancreas excised. The neck, at the level of the superior mesenteric vessels, was closed by a silk ligature. It was possible to excise the head without injury to the common duct as it entered the duodenum. The main pancreatic duct was ligated and divided at the point of entrance into the duodenal wall. The blood supply of the duodenum remained intact. Fourteen months later a second laparotomy was performed to inspect the upper abdomen. The liver appeared normal. The body and tail of the pancreas had become an elongated cystic structure with transparent walls. The site of the head of the pancreas was cicatrized but there had not been sufficient contracture to approximate the stump of the neck to the duodenal wall. There was no evidence of pancreatic regeneration from the duodenal wall at the site of the ligated distal stump of the duct of Wirsung (which apparently had atrophied).

The animal's condition remained satisfactory. He ate normally of the stock diet which consisted of bread, greens, bananas, lung stew, and sometimes milk. There was no diarrhea. On several occasions the fasting blood sugar was within normal limits. Early in March, 1944, he appeared to be ill and depressed. March 21, 1944, he was found dead in his cage.

Necropsy revealed pulmonary congestion. The abdomen contained no free fluid. The liver was grossly normal. The gall bladder and bile passages were normal. The alimentary canal was normal; there were no ulcerations. The site of the head of the pancreas was occupied by strands of fibrous tissue (Fig. 1). The body and tail of the pancreas had the appearance of an elongated cyst with translucent walls 4.5 cm. in length and 1 cm. in greatest diameter. On its surfaces were small,

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thin, irregular patches of dull yellowish tissue. The ligature at the neck of the pancreas was identified at the site of original placement. Inspection of the duodenal wall failed to reveal the site of the ligated terminal portion of the main pancreatic duct. There was no gross evidence of regenerated pancreatic tissue in the site previously occupied by the head of the pancreas. The neck of the pancreas was not approximated to duodenal or jejunal walls. There was no gross evidence of ducts from the occluded neck of the pancreas to bowel walls. The immediate cause of death was not apparent.

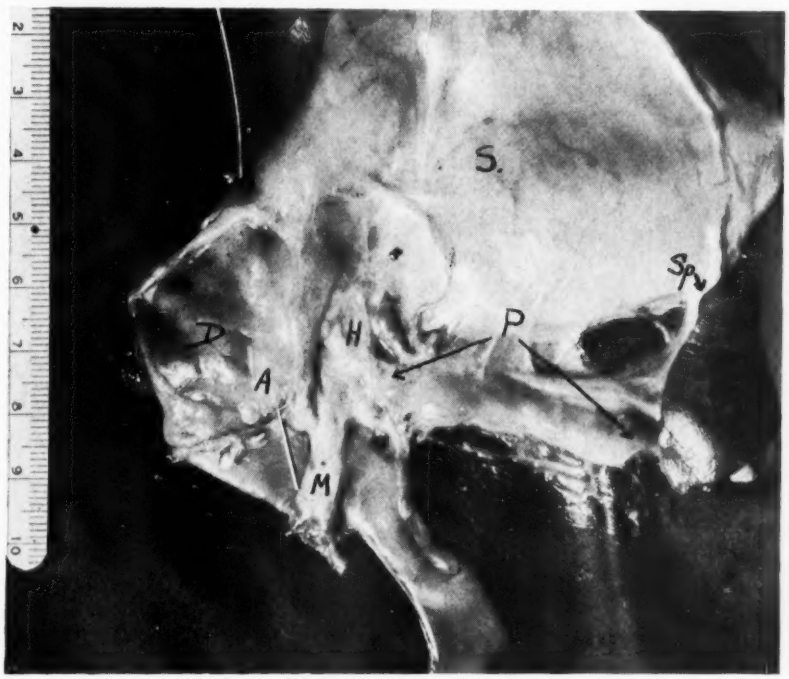

Fig. 1.—Necropsy specimen of *Macaca rhesus* monkey four years after excision of head of pancreas and ligation of stump. *S*, stomach; *Sp.*, spleen; *P*, body and tail of pancreas converted into elongated cyst; *D*, duodenum (opened) with metal probe in common bile duct protruding from ampulla, *A*; *H*, fibrous tissue in site previously occupied by head of pancreas; *M*, superior mesenteric vessels. There is no evidence of pancreatic parenchyma, nor evidence of ducts between the occluded neck of pancreas and bowel walls (jejunum, duodenum). The stump of the main pancreatic duct ligated near the duodenal wall four years previously has atrophied completely.

Histologic studies revealed normal liver. Sections through the duodenal wall in the region of the ampulla showed no evidence of pancreatic ducts or acini. Multiple sections through the cicatrized tissue at the site previously occupied by the head of the pancreas revealed no pancreatic acinar tissue nor ducts. Sections at the proximal tip of the cyst replacing pancreas showed no acinar tissue or proliferating ducts. The wall of the cyst, which contained a clear gelatinous fluid, was composed of fibrous tissue and exhibited clumps of ducts appended to some of which was an occasional clump of cells resembling a pancreatic acinus in resting stage. The walls also contained scattered islets of Langerhans.

DISCUSSION

In the monkey described, permanent atrophy of acinar tissue of the body of the pancreas followed excision of the head and ligation of the neck of this organ. Islets survived and apparently functioned to permit

normal carbohydrate metabolism. Contrary to observations reported for the dog, that regeneration of pancreatic tissue occurs from small fragments of such parenchyma that may remain on the duodenum or that may result from proliferation of the stump of the main duct, no evidence was found in this monkey that regeneration of acinar tissue occurred from the ligated terminal stump of the duct of Wirsung or that such regeneration occurred from the body of the pancreas occluded for a prolonged period (four years). Furthermore, in this animal there was no evidence of duct proliferation from ligated stump of the body toward the adjacent duodenal or jejunal walls.

Survival for four years of one monkey was thus possible in the absence of pancreatic acinar tissue and with the absence of external pancreatic secretion. There was no evidence of significant physiologic disturbances during this period.

HEMOSTATIC GLOBULIN AND PLASMA CLOT DRESSINGS IN THE LOCAL TREATMENT OF BURNS

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AND AUSTIN JOYNER, M.D., PEARL RIVER, N. Y.

CURRENT literature reveals a multiplicity of methods and theories in the local treatment of burns. The listing of at least thirty-seven different methods attests to some obvious confusion and inadequacy. The magnificent progress in systemic treatment made possible by basic discoveries in pathologic physiology and pharmacology have not been paced by similar improvement in local treatment. Recent return to favor of some of the older methods, such as petrolatum gauze and saline dressings, gives the impression that there is still much to be desired. Certainly no single treatment has been found satisfactory or applicable to all areas of the body even for burns of like degree.

Ideal local treatment should satisfy these criteria:

1. Trauma to the already damaged tissue must be minimal. This is particularly important for the remaining seeds of tissue since the damage can be repaired only by regeneration from this origin or by plastic replacement from others.
2. It should prevent plasma loss and other factors leading to shock.
3. It should be adaptable to the various requirements of function and structure of different parts of the body to insure good functional end results.
4. It should not predispose to nor trap infection.
5. Bacteriostatic activity and reduction of pain are essential.

It is believed that a plasma clot dressing has virtue because it may satisfy a maximal number of these principles. It is no more than an attempt to preserve the damaged tissue in a state conducive to rapid healthy recovery. It is no substitute for intelligent plastic surgery and certainly there is no desire to claim that results obtained are due to any dynamic properties of the method. Essentially the method consists of using a plasma clot to form a surgical dressing. The eschar covering the burned area is practically a physiologic dressing and should interfere minimally with the local physiology already disturbed by heat. The method is outlined here in order that its value may be quickly assessed in the hands of others.

Strips of sterile fine mesh gauze bandage (4 by 8 inches) are placed in a sterile basin. Preserved blood plasma from pools, banks, etc., is rapidly mixed with a solution having thrombic activity and then poured over the gauze in the basin. In a short time a plasma clot

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gels on the gauze. The burned area has previously been débrided and cleaned with dilute soap and saline solution after opening all vesicles. The gel impregnated gauze is then accurately layered over the burned area after sprinkling very lightly with sulfadiazine powder. Extreme care must be used to sprinkle the powder lightly and not allow clumping. Over the plasma clot dressing is then placed a snug dressing of sterile gauze reinforced with elastic bandage to provide pressure. The absorption of serum by the heavy gauze permits the dressing to dry in from six to twelve hours.

Results at this early date in a few patients with severe burns of the face, hands, and body have been more than gratifying. Pain has been uniformly absent. The dressing became stiff and adherent over healthy areas and remained so until softened and removed by wetting with saline solution. This, with pressure, prevented surface and tissue plasma loss and may have favored rapid and healthy epithelization. Infection has been absent or easily controlled since the plasmolytic action of bacteria allows easy detection by softening of the dressing. Such areas were readily lifted and treated. Although the clinical material with which to study this method has been limited, it is felt that the results to date justify a larger and more extensive trial.

The dressing has been prepared by several different methods. A preliminary dressing of plain plasma-soaked gauze in which the plasma was precipitated by chemical agents such as tannic acid and silver nitrate has been used. This method was discarded because the dressing became extremely hard and difficult to remove. The anticoagulant activity of sodium citrate in the plasma might be corrected by addition of calcium chloride. Since there are numerous objections to the use of any such chemicals in burned areas, thrombic activity has been employed to clot the plasma. This thrombic activity is obtained from a commercially prepared "hemostatic globulin" derived from rabbit's plasma and having the activity of thrombin. It has been found that 10 c.c. of 10 per cent solution of the hemostatic globulin will clot 100 c.c. of plasma firmly in from three to ten minutes. Since plasma preparations vary considerably, the strength of the plasma clot is controlled by varying the amount of hemostatic globulin and the time of action. The standard liquid intravenous human plasma which has been used might be replaced since the ability to clot and sterility are the only necessary prerequisites. Plasma containing precipitate making it unsatisfactory for intravenous use before filtering or plasma containing pyrogens could be employed. Either bovine or equine plasma, though untried, should be satisfactory if sterile. Both have been used intravenously in human beings. It is possible that a thicker and firmer clot could be obtained with a frozen or dried product by reconstituting it with a limited amount of water. The possibility of a mixture of powdered plasma and globulin impregnated on gauze is most attractive. The observation that the blister fluid in

several cases could be easily clotted prompted the use of the hemostatic globulin alone in several cases. This was also varied by spreading a plasma-moistened gauze dressing over the burned area and then spraying the gauze with the hemostatic globulin. If these variations are as successful as the heavier plasma clot method, they will represent a very practical saving of material. At this time they appear to be more practical for burns of a light degree.

SUMMARY

A method of preparation of a plasma clot dressing has been described and variations discussed. The method involves the clotting of plasma over gauze by means of hemostatic globulin. Plasma clot dressings prepared in this manner, and hemostatic globulin alone, have been used in the local treatment of burns. Encouraging early results indicate the desirability of further trial of these procedures.

TRANSLUMBAR AORTOGRAPHY—AN APPARATUS FOR INJECTING THE RADIOPAQUE MEDIA

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ONE of the fundamental requirements for the production of a satisfactory abdominal arteriogram is the adequate concentration of radiopaque media within the arteries at the instant the roentgenographic exposure is made.[1, 2] In order to accomplish this, 15 to 20 c.c. of the media must be injected into the aorta within four to six seconds. An apparatus capable of exerting three atmospheres (45 pounds) of pressure on the fluid to be injected has been found essential.

The apparatus* (Figs. 1 and 2) herein described is of simple construction, compact, easily sterilized, and accessible to anyone who can secure the services of a metal lathe operator. It is built about a one-quart blowtorch which serves to generate and supply the required pressure as well as support the cartridge in which the media is contained.

A one-half inch, three-way, airtight stopcock is screwed into the opening from which the heat-generating mechanism of the torch has been removed. To the horizontal nipple of the cock is attached, by means of a small, one-half inch brass elbow, an air gauge capable of registering 50 pounds of pressure. A one-half inch elbow is connected to the remaining opening in the cock. The cartridge, which contains the radiopaque media, is joined to the male end of this elbow by means of a tapered screw male and female coupling. The connection, which may be easily and rapidly adjusted with the bare fingers, insures an airtight union and at the same time is sufficiently strong to support the cartridge. The Luer lock, one way stopcock attached to the lower end of the cartridge, allows union with a piece of stiff tubing which in turn joins by Luer lock the cartridge to the needle inserted in the aorta.

The chamber in which the radiopaque media is placed is constructed about a thick-walled "urea tube" converted into a cylinder by grinding away the bottom. The cylinder is then snugly fitted into a jacket made from a piece of one-inch brass pipe in which two windows are cut opposite each other in order to allow adequate visualization of the media. Projection of each end of the cylinder, about one-sixteenth inch beyond the brass jacket, is arranged to allow proper cushioning of it against rubber gaskets contained in two brass caps which are screwed on each end of the metal jacket. The upper cap serves to support the cartridge as well as connect it with the pressure chamber. The lower cap supports a one-way stopcock with Luer lock. After the cartridge is assembled the glass cylinder is calibrated at 5 c.c. intervals.

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*Constructed by Terrell Supply Company, Fort Worth, Texas.

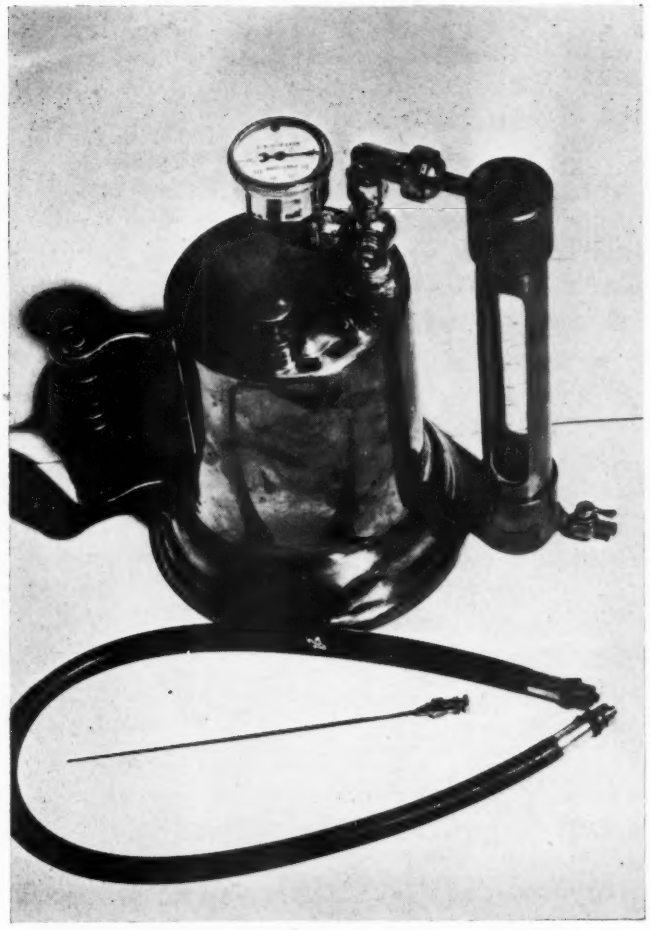

Fig. 1.—Photograph showing the pressure chamber and cartridge assembled.

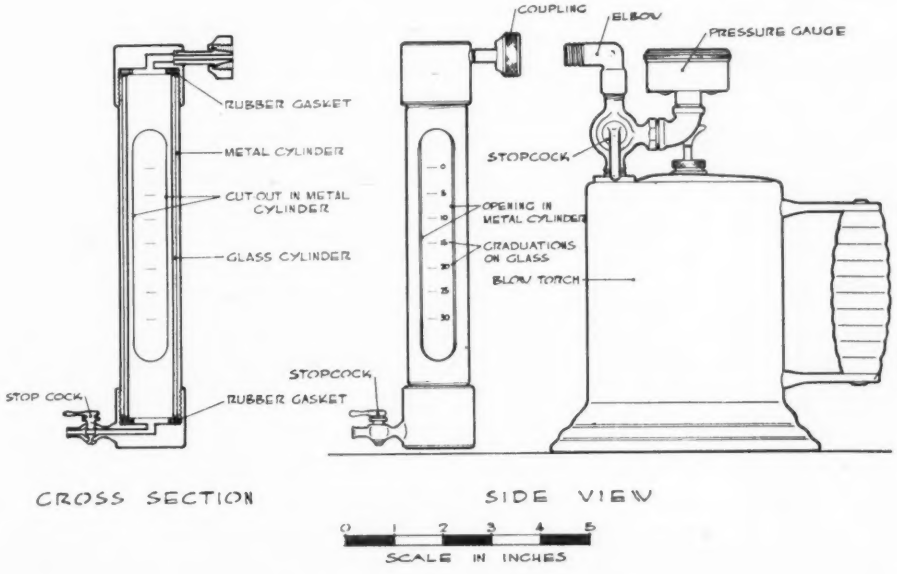

Fig. 2.—Sketch showing apparatus.

The capacity of the chamber is such that it will accommodate slightly more than 60 c.c. of fluid, an amount sufficient to provide a safe margin beyond the 15 to 20 c.c. of fluid to be injected, therefore reducing to a minimum the danger of introducing air into the aorta. Filling of the sterile cartridge is accomplished by locking the tubing to the one-way cock and injecting the media to the required level in the cylinder in a retrograde fashion. Expulsion of all air from the apparatus results at the same time. The one-way cock is then closed. With the tubing attached the cartridge is readily connected to the pressure chamber through use of the screw coupling. The 45 pounds of pressure generated in the torch by the built-in pump is then applied to the fluid by adjusting the three-way stopcock. The speed of the flow as well as the amount of fluid to be injected into the aorta is controlled by the one-way cock at the lower end of the cartridge.

The needle used to puncture the aorta is of special construction. It is made from 18 gauge stainless steel tubing and is 7 inches in length.

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Notice

References for the article on page 181 of the August, 1944, issue, "The Relationship of Hormones to Testicular Tumors" by Gray H. Twombly, M.D., New York, N. Y., will appear at the end of the reprints.

Editorial

The Story of the Kenny Method

JUST three and one-half years ago, in 1940, a distinct change in our treatment of infantile paralysis was introduced, one that has since caught the public's attention because of its human drama. This was, of course, the method of treating infantile paralysis victims which was evolved by Sister Kenny, the Australian nurse.

Many have misunderstood the nature of the Kenny treatment, and have thought it a cure for infantile paralysis. That is not true, and Sister Kenny makes *no* such claim. There is no cure for this crippling disease. The medical profession is still in the dark as to how to prevent it. It cannot control its spread. No one yet knows by what method this virus is carried from one victim to another. In a day when we are masters of malaria, smallpox, and diphtheria, infantile paralysis is still a riddle, a mystery, a crippling menace prowling our country at will.

What Sister Kenny *has* contributed, however, and it is a very real contribution, is a method for treating victims already stricken by infantile paralysis; a method that in the opinion of many American doctors reduces the crippling aftereffects of the disease.

There is a real interest in the history of the Kenny method in this country, and The National Foundation for Infantile Paralysis played an all-important part in evaluating this technique and in making it available to every infantile paralysis victim.

Sister Kenny went to the offices of the National Foundation one day in May, 1940, because she knew that the job of the National Foundation was to examine and study every new bit of knowledge that could possibly hasten the conquest of infantile paralysis. Present that day were Sister Kenny, the President of the National Foundation, and its Medical Director. Sister Kenny told how she had first developed her method. Thirty years before, as a young nurse in the Australian bush country, without medical assistance she had to care for a child stricken with infantile paralysis. Instead of immobilizing her patient's paralyzed limbs in casts or splints, she worked out a method of easing the pain and tightness in the muscles by frequent applications of heat—strips of woolen material were wrung out of steaming hot water. As the pain subsided she followed this with passive exercise until the patient himself could move his limbs. She felt that in many cases, this treatment had prevented many of the crippling aftereffects of the disease.

Sister Kenny was anxious that the National Foundation subject her method to scientific check, and so was the National Foundation. A few weeks later, when the University of Minnesota asked the National Foundation to support a program to study the Kenny method, it readily made a grant to that institution to enable Sister Kenny to demonstrate her method, and to give the doctors at Minneapolis a chance to see her work. For the next six or seven months, Sister Kenny treated infantile paralysis patients in Minneapolis.

In January of 1941, the National Foundation received a preliminary report from the doctors at the University. They were strongly impressed by what they had seen. To be sure, the number of cases studied had been few—too few to justify definite conclusions, but the physicians supervising this study felt that the patients treated had made far better recoveries than was usual in their experience. They recommended further study.

There was one fact, not widely known, that made these doctors cautious in their judgment. And that was the fact that over 50 per cent of all infantile paralysis patients seemingly recover by themselves, without any special form of treatment! "How do we know," these doctors asked, "That many of these patients Sister Kenny has treated might not have been among those that would have recovered spontaneously?" Obviously no one could answer that question, but medical science and the National Foundation had to take that factor into account.

The caution of these doctors making their first study of the Kenny method was justified on other grounds, too. They had seen many hopeful methods for treating infantile paralysis tried before—methods which failed to stand up under scientific test. Before they gave the Kenny method their full approval, they had to be sure.

That is why, in 1941, the National Foundation made a second grant to the University of Minnesota to make further studies of the Kenny method. Nearly 100 patients were treated the following year. In December of 1941, the medical men of the University made a second report. After consideration of this report, the Medical Advisory Committee of the National Foundation declared:

"It is the opinion of this committee that during the early stages of infantile paralysis the length of time during which pain and tenderness are present is greatly reduced, and contractures caused by muscle shortening during this period are prevented by the Kenny method. The general physical condition of the patient receiving this treatment seems to be better than that of patients treated by some of the other methods during a comparable period."

It was on the basis of this report that The National Foundation for Infantile Paralysis felt justified in opening the throttle and going full steam ahead to make this Kenny method of treating infantile paralysis available everywhere in the land. A plan was immediately set up to

instruct and train doctors, nurses, and physical therapy technicians. Sister Kenny herself was to help in the teaching at the University of Minnesota.

How well this has worked was clearly demonstrated during the epidemics of 1943 when 12,404 cases were reported. The doctors of the whole nation had learned something of the work; many were intimately acquainted with it. Physical therapy technicians and nurses had been trained to do the work. From the epidemic areas of the West, the Central States, and the East came a flood of requests from physicians for more technicians and more nurses to give this treatment.

Here was proof of the endorsement of the method by American medicine! Patients could be treated from coast to coast. Private physicians, clinics, hospitals, and departments of health called for more skilled workers. The supply was limited by the demands placed on this country by war; yet there were enough to do a good job.

Up to the present time, a total of 900 persons have received this training at the University of Minnesota alone, and have been graduated with the approval and certification of Sister Kenny.

All of this has been tremendously costly—a cost borne entirely by the National Foundation. To date, $107,000 has been given by the National Foundation to the University of Minnesota alone, to further the evaluation and teaching of the Kenny method. Every sum this University has ever requested has been granted in full by the National Foundation.

But the task of teaching the number of technicians needed to serve the whole country was too great for any one school. So the National Foundation opened other centers. Institutions in California, Illinois, Indiana, Georgia, Pennsylvania, and New York took up the teaching of the Kenny method. In addition to the money given to the University of Minnesota, $140,000 has been granted to the other schools. These grants were made to schools connected with or operated by medical teaching centers. Eight medical colleges and one hospital devoted solely to treating infantile paralysis and to training professional people took up the burden of making the special skills and knowledge available to all doctors, nurses, and physical therapy technicians. There was no quarrel here between American medicine and new methods of alleviating suffering and crippling from infantile paralysis!

The National Foundation has spent additional money on scholarships, wool for treatment, distribution of literature, exhibits, and demonstrations—a total of $301,000.

In fact, and it is one worth remembering, in the past three years the National Foundation and its Chapters have spent a total of over one-half million dollars of your money for the study and teaching of the Kenny method. It is no exaggeration to state that in all the history

of medicine, few new theories have ever received such generous financial support from the people of any nation.

In addition to all of the foregoing, two five-year grants have been made recently by the National Foundation: one for $175,000 to the University of Minnesota to study the physiologic problems concerning the mechanism of infantile paralysis and methods of treatment; the other for $150,000 to the University of Pennsylvania to establish a center for research and instruction in physical medicine. Both of these grants permit further evaluation and teaching of the Kenny method.

It is the dimes and dollars of the American people that have made this possible—the dimes and dollars they have contributed each year to the March of Dimes. And those dimes have done good work. Last year, the third greatest epidemic in the recorded history of the disease in the United States struck our country. Had it not been for the hundreds of doctors, nurses and technicians trained with the public's money and ready to administer the Kenny method promptly, that epidemic might have resulted in a national disaster.

It is obvious, of course, that this newer type of treatment is far more costly, in money and personnel, than the older systems of handling victims of poliomyelitis. Heretofore, patients were usually immobilized in splints and plaster casts and could be cared for by a small staff of doctors, nurses, and technicians. The physical therapy given usually consisted of a few hours of treatment a week, and that frequently was administered only late in the disease.

With the Kenny method, all that is different. Our medical men, in their own language, describe the Kenny method this way: "It is the early use of physical therapy, designed to prevent unnecessary deformities and to bring about the maximum function of such nerves and muscles as may have been spared by the disease process."

That means that each patient must have far more individual attention. Each must have hot packs applied every hour or two for at least twelve hours of the day during the acute stages of the disease. At the same time, the passive exercise and re-education of the patient's muscles must be started. Just consider the personnel required to provide such care under epidemic conditions. Consider, too, the soaring cost of such treatment.

Progress is being made in the fight against infantile paralysis. The Kenny method definitely represents an important step forward in our treatment of this disease. But the fact that it *is not* a cure and it is not fully developed must be borne in mind.

There are some patients who cannot be helped at the present time by any known method of treatment, whether it be the Kenny method or any other. These are the victims whose nerve cells have been completely destroyed by the ravages of the disease. To them, motion in some muscles has been denied forever. It is for these cases, particularly, that the

research programs of the National Foundation, designed to find a way to prevent the disease, must go on.

Unfortunately, no one has yet been able to find a cure for infantile paralysis. Studies are constantly being pursued along this line by the National Foundation, but so far without result. There is no known drug or serum or vaccine to combat the virus that causes the disease. But, in the meantime, both the amount and kind of palliative treatment have been improved.

How such treatment methods can be best taught and made available to the people is a matter about which there is a difference of opinion. The establishment of a Kenny institute in Minneapolis as the only place where the Kenny method would be taught has been suggested. But, of course, it is impossible to train all the Kenny technicians we require at any one place, in Minneapolis or elsewhere. And it would be equally impossible for any one person to supervise the various centers of teaching now supported by The National Foundation for Infantile Paralysis.

The ultimate aim is to make whatever is sound in the Kenny method a part of the curriculum of every medical, nursing, and physical therapy school in the country—and that aim will be accomplished. No one institution can have a monopoly on the teaching of the Kenny method. While it is Sister Kenny's contribution to humanity, for humanity's sake it must be available to all.

This history of the Kenny method shows very clearly that the National Foundation stands ready to evaluate and test and make available every method of treatment that promises to loosen the grip that infantile paralysis has on our children. If, on the basis of tests made, a method is found effective, the full resources of The National Foundation for Infantile Paralysis will be thrown behind it. The one-half million dollars of your money spent on the Kenny method to date certainly proves that.

The National Foundation for Infantile Paralysis is your Foundation—a Foundation dedicated to one purpose and one purpose only—final and complete conquest of infantile paralysis.

Until that conquest is made, the National Foundation will carry on the most ambitious research program ever marshaled against any disease. It will also continue to provide hospitalization and medical care, including the Kenny treatment, in every community to every infantile paralysis victim who needs it. And it will continue to evaluate and aid every new method that is brought to its attention.

It is the people of America who have made all that possible!

—*The National Foundation for Infantile Paralysis, Inc.*
New York, N. Y.

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

TERMINAL HEMORRHAGIC SHOCK

CIRCULATORY DYNAMICS, RECOGNITION, AND TREATMENT

K. G. KOHLSTAEDT, M.D., AND IRVINE H. PAGE, M.D., INDIANAPOLIS, IND.

(From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital)

CONTEMPORARY evidence proves beyond doubt that treatment of early hemorrhagic shock, even when severe, by plasma or whole blood, is most satisfactory. From the practical viewpoint of restoring circulation it is probable that only minor modifications will be made in the near future to improve it. On the other hand, terminal hemorrhagic shock has received much less study and its management can surely be improved. As McMichael puts it, "It seems that under battle conditions this irreversible state may constitute the major problem of shock owing to the unavoidable delays in getting the patient back to base hosptials. The problem is therefore both urgent and practical."

Those of us who have managed only relatively small numbers of major accidents in civilian practice have seen examples of patients in extremis from loss of blood, to whom either plasma could not be administered at all for lack of time or, more commonly, the patient died after the first bit of plasma ran in. It was to study this question that our investigation was undertaken.

To overcome certain of the difficulties of administering plasma or blood by vein when the patient was dying, we investigated, in 1942, the possibility of administering it by artery instead of by vein (Kohlstaedt and Page). This method proved to have advantages. The artery (femoral preferable) can and should be exposed without delay, avoiding the often futile search for collapsed veins. Plasma is administered under a fixed pressure, hence the initial rate of infusion is rapid while the amount infused is automatically controlled by the circulatory system itself. For example, when the pressure is set at 50 mm. Hg, plasma flows in until the pressure in the circulatory system reaches this level. Under this circumstance the arterial pressure is restored more rapidly than when plasma is given by vein so that precious minutes are saved which may spell the difference between success or failure. An additional advantage was found in that about one-half as much plasma was required to restore the circulation as when plasma was given by vein.

We were not convinced at that time that criteria had been found surely indicating lack of survival when all of the blood that had been removed was returned. A few animals survived contrary to predictions based on our criteria. In short, the great individual variations among the animals proved a more and more important handicap as the severity of shock was increased.

From clinical observations we have never been convinced, despite the statement, now almost an aphorism, that shock is wholly peripheral circulatory failure, and its corollary, that the heart is normal in shock. For this reason we sought methods of demonstrating in late shock failure of the heart to perform its functions adequately.

Wiggers and Werle (1942) have recently shown in an important study that after prolonged hemorrhagic hypotension the capacity of the ventricles to respond to a given venous pressure (stretch) is reduced and that this hypodynamic state is masked when venous pressure declines concurrently. Prolonged reduction in coronary flow is suggested as the cause. Their results strongly suggest that reduced capacity of the myocardium to respond to given venous pressures is one of the factors which precipitates an irreversible circulatory state.

In burn shock, study of the circulatory dynamics showed that during the terminal phase the heart as well as the blood vessels became refractory to stimulating drugs (Page). They seemed exhausted. It was not unreasonable to suppose that the same might occur after prolonged hemorrhage, hence we turned to use of the cardiometer as the best method at hand for demonstrating cardiac injury. It has not only supplied us with a criterion for terminal shock but, as a result of study of the sequence of events after hemorrhage, pointed to the needs in treatment of the condition. The study on animals is reported in this communication and the clinical experience will be reported in another.

METHODS

Dogs weighing 12 to 20 kg. were not fed for twenty-four hours and then anesthetized by the intraperitoneal injection of 30 mg. per kilogram of sodium pentobarbital. The carotid artery was dissected out and a glass cannula inserted, which was connected by a Y tube to two mercury manometers. One manometer recorded arterial pressure on a slow-moving kymograph which ran continuously during the experiment and the other recorded on a rapidly moving one which was operated at short intervals for the purpose of recording the movements in the cardiometer. A metal cannula was inserted into the trachea for artificial respiration during the period the thoracic cavity was open. A glass cardiometer was placed about the heart through an opening in the chest wall which had been made by careful resection of the left fifth rib. A glass tube was extended from the pleural cavity through the chest wall and then each layer of tissue was sutured around this tube and the stem of the cardiometer. The cardiometer and tube from the pleural cavity were

connected to a differential manometer (Boyd and Patras, 1941)* and negative pressure was established within the thoracic cavity, cardiometer, and chambers of the differential manometer. (The details of the application and construction of the complete apparatus for use of a cardiometer with a closed chest will be described in a separate communication.)

When negative pressure had been restored, artificial respiration was discontinued and the animal breathed spontaneously. Respirations were recorded on the drum of a kymograph by means of a tambour connected to the tube leading from the pleural cavity. A water manometer was also connected to this tube to measure the intrathoracic pressure. This pressure was maintained at the same level present before the chest was opened. Changes in intrathoracic venous pressure were recorded by inserting a No. 12 rubber catheter down the right external jugular vein until its tip was in, or very near, the right atrium. The catheter was filled with heparin solution and connected to a water manometer. A long shellacked cork served as a float for the manometer and thus it was possible to record changes in venous pressure on the drum.

The femoral vein and artery were dissected out and glass cannulae inserted. The cannula in the femoral artery was connected to the apparatus for withdrawing blood and the vein was connected to the reservoir of this apparatus so that blood could be returned. This apparatus and the method of producing sustained posthemorrhagic hypotension has been described by us (Kohlstaedt and Page, 1943). Ten per cent sodium citrate was used as anticoagulant and great care was exercised in preventing an excess of it in the blood in the reservoir.

EFFECT OF PROLONGED POSTHEMORRHAGIC HYPOTENSION ON CIRCULATORY DYNAMICS

The change in stroke-volume, cardiac output, heart size, and venous and arterial pressure which result from intermittent bleeding are schematized in Fig. 1.† The uppermost tracing represents the record from the cardiometer, the upper margin of which records diastolic volume and the lower margin systolic volume. The distance between is equivalent to stroke volume. The next lower tracing represents intrathoracic venous pressure (millimeters of water) and below this is recorded arterial pressure (millimeter of mercury). The vertical dotted lines represent the points at which blood was withdrawn or injected, the

*We wish to thank Dr. T. E. Boyd for his gracious aid in the construction of the cardiometer.

†The actual values for cardiac output during the course of the experiment which has been schematized in Fig. 1 are: at *A*, prehemorrhagic control, average stroke volume 16 c.c., heart rate 100 per minute, and cardiac output 1.8 liters per minute. At *B*, the point of maximum reduction in heart size, the average stroke volume was 5.6 c.c., the rate 150 per minute, and cardiac output 0.8 liter per minute. At *C*, after considerable cardiac dilatation had occurred and arterial pressure had fallen progressively, average stroke volume was 4 c.c., heart rate 160 per minute, and cardiac output 0.6 liter per minute. At *D*, after a second injection of 35 c.c. of blood had been given intra-arterially, average stroke volume was 3.6 c.c., heart rate 80 per minute, and cardiac output 0.28 liter per minute. Finally at *E*, the point of extreme cardiac dilatation and arterial pressure rapidly declining despite a third injection of 35 c.c. of blood intra-arterially, the average stroke volume was 3 c.c., heart rate 100 per minute, and cardiac output 0.3 liter per minute.

amount in cubic centimeters being given at the top of the chart. The total amount of blood removed is indicated by the shaded area at the bottom.

Let us illustrate the course of events by describing a typical experiment. Following the first three hemorrhages, stroke volume, cardiac size (diastolic volume), venous pressure, and arterial pressure all declined sharply to be followed within twenty minutes by a rise in venous and arterial pressure. Stroke volume and cardiac size, however, remained reduced. As the amount of each hemorrhage became smaller, changes in arterial and venous pressure were less pronounced. Heart

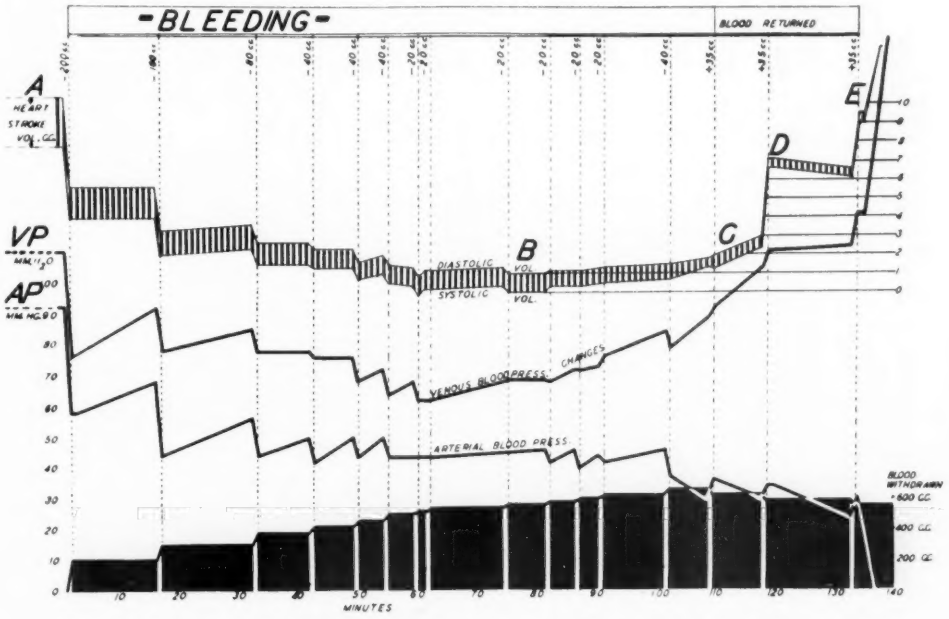

Fig. 1.—Schematic diagram of the effect of hemorrhage and prolonged hypotension on circulatory dynamics. *A*, Cardiometer record of stroke volume in prehemorrhagic period. *B*, Point of greatest reduction of diastolic and systolic volume. *C*, *D*, and *E*, 35 c.c. of blood injected intra-arterially. *VP*, Intrathoracic venous pressure in millimeters of water. *AP*, Arterial pressure in millimeters of mercury.

Shaded area denotes total amount of blood removed (scale at right side). Scale at upper right indicates stroke volume units of cardiac dilatation.

size continued to decline until at point *B* it was minimal. Fixed hypotension was established at 46 mm. Hg. During the twenty minutes of hypotension preceding point *B*, venous pressure rose steadily and continued to rise in spite of further withdrawal of blood. Five minutes after the maximum decrease in cardiac size had occurred, both systolic and diastolic volume began to increase and this was not affected by further withdrawal of two 20 c.c. and one 40 c.c. portions of blood. The rise in systolic volume was more rapid than rise in diastolic so that stroke volume grew smaller as dilatation progressed. These cardiodynamic changes were accompanied by marked reduction in heart rate in all experiments. One hundred minutes after the initial bleeding,

following the removal of another 40 c.c. portion of blood, arterial pressure fell precipitously and at *C*, 35 c.c. of blood were returned intra-arterially. A very brief rise in arterial pressure occurred but the rate of cardiac dilatation and increase in venous pressure were not reduced. A second injection of blood at *D* produced even less rise in arterial pressure and was followed by a very marked rise in both systolic and diastolic volume. Cardiac size and venous pressure were maintained for about ten minutes but the arterial pressure declined steadily, and at *E* a third injection of 35 c.c. of blood was given. This was followed by a sharp increase in heart size, concomitant rise in venous pressure, and precipitous decline in arterial pressure. Death ensued at this point.

Similar changes in circulatory dynamics were observed in twenty-seven experiments and the results are shown in Tables I to III. The stroke volume, heart rate, cardiac output, and arterial pressure were recorded at five points in each experiment. These were: I, during the prehemorrhagic period; II, during hypotension, the point at which maximum reduction in cardiac size occurred; III, at the completion of the hypotensive period, that is just before treatment began; IV, immediately after treatment ended; V, after circulation had become stabilized, that is from fifteen to sixty minutes after treatment had been completed. Changes in venous pressure and diastolic volume were measured at points II to V.

The changes which are typical of prolonged posthemorrhagic hypotension are summarized in Table IV.

These changes, as observed in the kymograph record of a typical experiment, are illustrated in Fig. 2. This figure is composed of sections of the record taken at each of the crucial points in an experiment. Section *I* is from the prehemorrhagic period; section *II* was taken 100 minutes later when hypotension had been established and there was a maximum reduction in cardiac size. This is indicated by the decline in systolic volume (lower margin of the cardiometer record) from line *X* to *Y*. The stroke volume had decreased from 13 to 5 c.c., heart rate from 150 to 130, and cardiac output from 2 to 0.6 liters per minute. Venous pressure had declined 5 cm. of water and arterial pressure remained at 40 mm. Hg. The increase in rate and depth of respiration is shown by the uppermost tracing on this record. Hypotension was continued for another twenty-two minutes and the changes which occurred in circulatory dynamics are shown by Section *III* (Fig. 2) at *T*. The increase in cardiac size is indicated by the return of systolic volume to line *X* from line *Y*. Stroke volume declined from 5 to 4.3 c.c., heart rate from 120 to 80 per minute, cardiac output from 0.6 to 0.3 liter per minute. Venous pressure rose 1 cm. of water and arterial pressure declined to 24 mm. Hg. There was a marked decrease in depth and rate of respiration. At *T*, 20 mg. of tuamine were injected. The changes produced will be discussed in another section of this communication.

The time required before cardiac dilatation occurred varied widely and was not correlated with the amount of blood removed. For example, in Exp. 66, Table I, cardiac dilatation did not occur after 185 minutes of hypotension which had been produced by the removal of 530 c.c. of blood (equivalent to 4.6 per cent body weight) but in Exp. 89, Table I, 2.6 stroke volume units of dilatation were present after forty-seven minutes of hypotension, and in Exp. 63, Table I, 105 minutes had elapsed before the same degree of dilatation occurred. Another example of the complete lack of correlation between these factors is found in Exp. 77, Table II, in which a quantity of blood equal to 4.6 per cent of body weight was removed; 125 minutes of hypotension resulted in 1.6 units of dilatation, while in Exp. 99, Table II, the removal of blood equal to 2.2 per cent of body weight, and fifty-seven minutes of hypotension produced 3.2 units of dilatation.

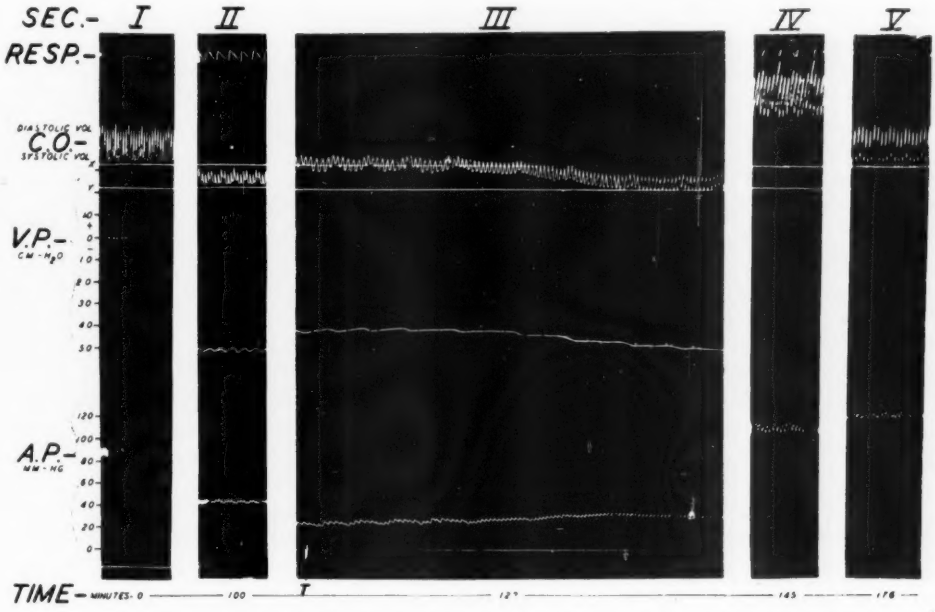

Fig. 2.—Treatment of posthemorrhagic shock after onset of cardiac dilatation by preceding the infusion of blood with the injection of tuamine. *Resp.*, Record of rate and depth of respiration; *CO*, record of cardiometer; *VP*, intrathoracic venous pressure in centimeters of water; *AP*, arterial pressure in millimeters of mercury; *X*, level systolic volume in prehemorrhagic period, and *Y*, level during maximum constriction of heart.

Section I, prehemorrhagic period; Section II, 100 min. later, during hypotensive period when greatest reduction in systolic volume was observed; Section III, 22 min. later in hypotensive period when cardiac dilatation was present; *T*, 20 mg. tuamine; Section IV, immediately after infusion; Section V, 30 min. after. Speed of kymograph, 1.8 cm. = 6 sec.

In eleven experiments the circulation time was measured at intervals during the hypotensive period by the intravenous injection of 0.3 c.c. of a 0.5 per cent solution of NaCN. The results (Table V) indicate that during the state of bleeding the circulation time is prolonged but as hypotension is established it is temporarily improved, that is it is

TABLE

TREATMENT OF TERMINAL POSTHEMORRHAGIC

EXP. NO.	DOG'S WEIGHT (KG.)	C.C. OF BLOOD REMOVED	BLOOD LOSS ≡ % BODY WEIGHT	DURATION OF HYPOTENSION (IN MIN.)	C.C. OF BLOOD INFUSED	RATE OF INFUSION (C.C./MIN.)	STROKE VOL. (C.C.)					HEART RATE PER MIN.				
							I*	II	III	IV	V	I	II	III	IV	V
66	11 5	530	4 6	185	530	26	9	5	4	14	22	160	110	120	60	70
62	12	465	3 8	137	235	34	28	18	15	22		120	90	100	80	
63	11 2	345	2 6	105	100	35	10	5	4 7	±2		120	130	120	70	
69	13 8	600	4 1	112	135	27	14	3 6	5 6	4 1		150	120	160	70	
89	14	300	2 1	47	180	36	9	4 5	5			160	150	80		
90	14	520	3 7	74	160	26	11 5	7 6	7 0	8		150	130	90	50	
76	14	620	4 5	134	none	none	16	5 6	3 3			110	150	80		

*Period in experiment at which observation was made.
I, During prehemorrhagic period; II, point at which maximum reduction in cardiac size occurred during hypotension; III, point just before treatment began after onset of cardiac dilatation; IV, immediately after treatment; V, fifteen to sixty minutes after treatment.

TABLE

TREATMENT OF TERMINAL POSTHEMORRHAGIC HYPOTENSION BY THE

EXP. NO.	DOG'S WEIGHT (KG.)	C.C. OF BLOOD REMOVED	BLOOD LOSS ≡ % BODY WEIGHT	DURATION OF HYPOTENSION (IN MIN.)	C.C. OF BLOOD INFUSED	RATE INFUSION (C.C./MIN.)	AMT. TUAMINE (MG./KG.)	STROKE VOL. (C.C.)					HEART RATE PER MIN.				
								I*	II	III	IV	V	I	II	III	IV	V
71	14 3	600	4 2	42	564	40	1 4	20	6 4	5 6	9 1	12	190	160	110	160	160
73	12 5	480	3 9	83	480	34	1 6	18	10	3 7	22	22	130	130	90	100	110
75	11 5	310	2 7	64	310	34	1 7	13	6 3	4 0	19	17	140	150	130	140	130
77	12	550	4 6	125	550	36	1 6	13	5	4 3	8 5	20	150	130	80	100	100
82	12	410	3 4	76	410	20	1 6	7	4 4	4 0	14	12	160	120	50	130	130
99	14	320	2 2	57	320	45	2 1	11 4	7 7	8 3	13 4	11	140	110	70	120	140
101	14	470	3 3	125	470	42	2 0	14 2	7 3	10 4	19	16	140	110	60	110	130
105	11	340	3 0	117	340	42	2 0	14	8 2	*8 0	15	12	120	160	130	160	180
106	12 1	435	3 6	100	405	58	2 0	15	7 6	4	24	13	170	150	70	110	110
109	16	640	4 0	65	575	44	2 0	16	7 8	7 2	16	17	170	130	110	150	180

†Spontaneous breathing stopped.

TABLE

TREATMENT OF TERMINAL POSTHEMORRHAGIC HYPOTENSION BY THE ADMINISTRATION

EXP. NO.	DOG'S WEIGHT (KG.)	C.C. OF BLOOD REMOVED	BLOOD LOSS ≡ % BODY WEIGHT	DURATION OF HYPOTENSION (IN MIN.)	DRUG USED	AMT. MG./KG.	C.C. OF BLOOD INFUSED	INFUSION RATE (C.C./MIN.)	AVERAGE STROKE VOL. (C.C.)					HEART RATE PER MIN.				
									I*	II	III	IV	V	I	II	III	IV	V
84	15 3	400	2 6	53	4-amine	1 9	400	40	12	5	7	19	16	110	120	100	140	150
86	12 0	290	2 4	56	4-amine	2 5	290	20	14	5	5	10	14	130	120	100	100	140
87	13 0	340	2 5	47	4-amine	1 5	150	30	13	4	2			150	120	80		
88	12 0	400	3 3	128	4-amine	2 5	400	36 3	19	4	2 7	24	16	130	140	100	100	110
97	13 5	580	4 2	55	1-amine	2 0	580	29 0	16	5 1	5	14 7		120	170	120	50	
98	15 4	570	3 7	80	1-amine	2 0	80	26 6	14	7 5	7 3			140	150	90		
94	18 0	620	3 2	51	paredrine		580	32	9	4 6	4	11	11	130	120	80	120	140
96	12 3	400	3 2	84	paredrine		none	none	10 5	6 6	3 5			160	120	70		
91	12 5	440	3 5	80	1-10,000 adren.	30 gamma	140	46	10	5 5	8	10		150	140	60	90	
92	12 8	395	3 1	75	1-1,000 adren	1000 gamma	345	38	10	5	±2	9		150	170	100	70	

I

HYPOTENSION BY INFUSION OF BLOOD ALONE

CARDIAC OUTPUT (L./MIN.)					ARTERIAL PRESSURE (TYP. HG.)					CHANGE VENOUS PRESSURE (CM. H_2O)				CHANGE DIASTOLIC VOL. (MM.)				INCREASE SYSTOLIC VOL.	STROKE VOL. UNITS	CIRCULATION
I	II	III	IV	V	I	II	III	IV	V	II	III	IV	V	II	III	IV	V			
1 4	0 5	0 5	0 8	1 5	100	42	44	50	84	−4 5	+0 1	+12	−4	−10	+11	+53	−34	none	none	Restored
3 4	1 6	1 5	1 8		100	72	44	36		−5	+1 8	+6		−11	+13	+27		3	0 16	Died
1 2	0 6	0 5	0 14		106	50	40	26		−1 0	+0 8	+4 5		−11	+9			13	2 6	Died
2 2	0 4	0 9	0 3		110	54	42	22		−7 4	+3 7	+11 7		−20	+14	+9		16	4 4	Died
1 4	0 6	0 4			102	40	34	18		−4 2	+0 6	+9 4		−15	+13	+39		12	2 6	Died
1 7	1 0	0 36	0 4		92	40	28	22		−5 0	+1 0			−12	+10	+31		12	1 5	Died
1 8	0 8	0 3			92	38	24			−3 8	+3 2	+2 6		−15	+32				10 5	Died

II

ADMINISTRATION OF TUAMINE SULFATE AND INFUSION OF BLOOD

CARDIAC OUTPUT (L./MIN.)					ARTERIAL PRESSURE (MM. HG.)					CHANGE VENOUS PRESSURE ON WATER				CHANGE DIASTOLIC VOL. (MM.)				EQUIV. SYSTOLIC VOL. CHANGE	STROKE VOL. UNITS	CIRCULATION
I	II	III	IV	V	I	II	III	IV	V	II	III	IV	V	II	III	IV	V	III		
3 8	1 6	0 6	1 4	1 9	138	46	24	78	96	−8	+7	+5	−2	−23	+24	+43	−42	+28	4 3	Restored
2 3	1 3	0 3	2 2	2 4	86	44	24	106	110	−4	+0 1	+6	+4	−4	+10	+30	−12	+10	1 0	Restored
1 8	0 9	0 5	2 6	2 2	96	42	32	120	80	−3	+2 5	+6	+6	−15	+7	+21	−5	+15	2 4	Restored
2 0	0 6	0 3	0 8	2 0	88	42	24	52	118	−6	+2 0	+7 0	−4	−20	+12	+10	−10	+8	1 6	Restored
1 1	0 5	0 2	1 8	1 5	112	58	32	110	124	−4 3	+12	−5	−9	−14	+43	−15	−23	+50	11 3	Restored†
1 6	0 8	0 6	1 6	1 5	98	46	20	150	118	−12	+1 1	+11	−8 8	−10	+22	+28	−20	+25	3 2	Restored
2 0	0 8	0 6	2 1	2 1	104	48	30	100	98	−4 5	+3 6	+6 5	−4 5	−13	+15	+35	−33	+15	2 0	Restored†
1 7	1 3	1 0	2 5	2 1	82	42	20	80	90	−1 9	+0 7	+4 3	−1 9	−22	+14	+4	−7	+7	0 85	Restored†
2 5	1 1	0 3	2 6	1 4	110	42	20	118	114	−3 4	+2 4	+1	−6	−25	+21	+54	−32	+28	3 7	Restored†
2 7	1 0	0 8	2 4	3 0	126	42	30	118	100	−7	+2 2	+10 8	−5 3	−22	+20	+35	−32	+26	3 3	Restored†

III

OF ONEAMINE, FOURAMINE, PAREDRINE, ADRENALIN AND INFUSION OF BLOOD

CARDIAC OUTPUT (L./MIN.)					ARTERIAL PRESSURE (MM. HG.)					CHANGE VENOUS PRESSURE (CM. H_2O)				CHANGE DIASTOLIC VOL. (MM.)				INCREASE SYSTOLIC VOL. (PER MIN.)	STROKE VOL. UNITS	CIRCULATION
I	II	III	IV	V	I	II	III	IV	V	II	III	IV	V	II	III	IV	V			
1 3	0 6	0 7	2 6	2 4	140	70	50	142	150	−4	+8	−0 5	−2 5	−21	+27	−4	−1 4	25	3 5	Restored
1 8	0 6	0 5	1 0	1 96	80	30	28	72	86	−7	+4	−3	−1	−30	+21	−8	−5	17	3 4	Restored
1 5	0 5	0 16		1	98	38	26			−2	+1 7	+3		−5	+10			20	5 0	Died
2 4	0 5	0 27	2 4	1 76	92	38	28	160	120	−4	+1	+10	−3	−28	+16	+10	−6	12	3 0	Restored
2 0	0 87	0 6	0 73		110	50	38	46		−5 4	+4 2	+12		−44	+9	+37		13	2 5	Died
1 96	1 13	0 6			102	42	30			−5 2	+2 8			−21	+23			25	3 3	Died
1 2	0 56	0 3	1 3	1 5	118	46	34	120	120	−4	+1 6	+5 8	+3	−23	+13	+3	+10	16	3 47	Restored
1 7	0 8	0 24			84	40	22			−1 5	+1 9			−6	+4			11	1 6	Died
1 5	0 8	0 5	0 9		86	42	30	30		−3 4	+2 6	+4 8		−12	+10	+8		10	1 8	Died
1 5	0 85	0 2	0 63		90	44	28	30		−23	+7	+9		−8	+16	+7		25	5 0	Died

TABLE IV

CHANGE IN:	FROM PREHEMORRHAGIC STATE (I) TO THE POINT DURING HYPOTENSION AT WHICH MAXIMUM REDUCTION IN CARDIAC SIZE APPEARED (II)	FROM POINT II TO END OF HYPOTENSIVE PERIOD (AFTER CARDIAC DILATATION, III)
Stroke volume	Decreased, average 51 per cent	20 decreased 6 increased Mean, 9 per cent
Heart rate	In 16 decreased In 10 increased	25 decreased 1 slight increase
Cardiac output	Decreased, average 54 per cent	Decreased, average 31 per cent
Venous pressure	Decreased, average 4.4 cm. H_2O	Increased, average +2.7 cm. H_2O
Diastolic volume (Cardiometer record)	Decreased, average 17 mm.	Increased, average +16 mm.

shortened. However, as cardiac dilatation appears and venous pressure rises, the circulation time again grows longer.

Treatment by intravenous infusion of all of the blood removed was uniformly successful and easily accomplished provided the infusion was begun before the onset of cardiac dilatation (point *B*, Fig. 1 or Section *II*, Fig. 2). If the infusion was delayed until onset of cardiac dilatation (Section *III*, Fig. 2) it was seldom successful and the animal succumbed before it could be completed. It was, therefore, obvious that before undertaking a comparative study of different agents for the treatment of the terminal stage of hemorrhagic shock, it was imperative that a satisfactory criterion for estimating the effect of hypotension on the cardiovascular system be established.

SELECTION OF A CRITERION FOR ESTIMATING SEVERITY OF SHOCK

Criteria such as withdrawal of a specified quantity of blood, reduction of arterial pressure to a fixed level, and maintenance of the pressure at this level for a certain length of time have proved in our experience to be inadequate because some animals can tolerate blood loss and hypotension much better than others.

In our previous study in which the intra-arterial infusion was compared with the intravenous method (Kohlstaedt and Page, 1943) the lack of pressor response to 0.3 c.c. of 1:10,000 adrenalin was used as a criterion but in these experiments some of the dogs could be saved by the intravenous infusion of all of the blood that had been withdrawn. The most that could be said was that refractoriness to the pressor effects of adrenalin greatly jeopardized the chances of survival after transfusion. Therefore this criterion could not be used for our present study because we wished to continue hypotension in *all* experiments until the animal could no longer be saved by the intravenous infusion of blood.

Another criterion of irreversible shock which has been used by some investigators in recent studies is the absence of a pressor response to

TABLE V

EFFECT OF POSTHEMORRHAGIC HYPOTENSION ON CIRCULATION TIME

	PREHEMORRHAGIC PERIOD			HYPOTENSIVE PERIOD													
				SOON AFTER BLEEDING				MAX. REDUCTION HEART SIZE				TERMINAL PHASE—CARDIAC DILATATION PRESENT				AFTER TREATMENT—CIRCULATION RESTORED		
EXP. NO.	ART. PRES. (MM. HG)	C. O. (L. PER MIN.)	CIRCULATION TIME (IN SEC.)	DURATION OF HYPOTENSION (IN MIN.)	ARTERIAL PRESSURE (MM. HG)	C. O. (L. PER MIN.)	CIRCULATION TIME (IN SEC.)	DURATION OF HYPOTENSION (IN MIN.)	ART. PRES. (MM. HG)	C. O. (L. PER MIN.)	CIRCULATION TIME (IN SEC.)	DURATION OF HYPOTENSION (IN MIN.)	ARTERIAL PRESSURE (MM. HG)	C. O. (L. PER MIN.)	CIRCULATION TIME (IN SECONDS)	ARTERIAL PRESSURE (MM. HG)	C. O. (L. PER MIN.)	CIRCULATION TIME (IN SEC.)
62	100	3.4	16	14	72	1.6	28	31	44	1.8	24	135	36	1.8	29			
63	106	1.2	30	26	50	0.6	64	102	40	0.6	60	133	42	0.7	40			
64	132	1.3	24	38	54	0.56	50	71	40	0.68	36							
66	100	1.4	17	55	42	0.5	43	181	44	0.5	29	235	30	0.6	68			
68	84	1.2	11	6	38	0.98	25	52	38	0.7	23	89	38	0.9	26			
69	110	2.2	14	19	48	0.8	71	54	42	0.9	51							
70	90	2.5	18	33	42	1.4	66	38	42	1.2	58							
71	138	3.3	24	6	46	1.3	27	25	40	0.6	31					96	1.9	16
73	80	2.6	16	7	44	1.4	21	45	38	1.0	27	72	30	0.6	37	106	2.2	15
74	108	3.0	18.3	14	42	1.7	20	55	38	1.5	16	82	36	0.9	25			
67	118	2.2	21	45	40	0.5	43	60	46	0.8	30	123	42	0.9	37			

the injection of 2.5 c.c. per kilogram of whole blood. However, we were able to save some dogs after the requirements of this criterion had been fulfilled. Furthermore, in some experiments the hypotensive period was continued for fifteen or twenty minutes after a test dose of blood failed to give a pressor response and at the end of this time the injection of blood was repeated. The second injection produced a rise in arterial pressure although the initial injection had failed.

We had observed that stroke volume in most instances of very severe shock was reduced about 70 per cent; hence, an attempt was made to use this as a criterion, but it too was unsatisfactory, because in five experiments in which it had been reduced an average of 64 per cent, normal circulation was restored by intravenous administration of citrated whole blood.

Another observation was that the intravenous method of readministering blood *never failed* if treatment was begun before the phase of cardiac dilatation occurred. If hypotension was continued until *slight* cardiac dilatation had occurred, then the administration of blood was an inadequate form of treatment.

From this observation it was evident that the degree of cardiac dilatation might serve as a criterion for the stage of shock not successfully treated by infusion of blood alone. If the criterion was to be useful, some method was necessary for expressing the amount of dilatation present at the time treatment was instituted. For this purpose we employed as a unit the *height* of the cardiometer tracing, that is the stroke volume, at that period in the experiment when cardiac dilatation could first be detected (*B*, Fig. 1). The distance is measured from the lower margin of the cardiometer tracing to a base line established by extending a line from the level of systolic volume at the time cardiac dilatation begins. When the lower margin has risen to a point which is equal to the height of the stroke volume, one unit of dilatation has occurred. This is illustrated in Fig. 1. The scale along the right margin of the cardiometer tracing refers to units of cardiac dilatation. At *C* two units of cardiac dilatation are represented, at *D*, seven units, and at E, ten units.

The following illustrates the use of stroke volume units. In Exp. 76, Table I, no attempt was made to treat the dog, and it died when cardiac dilatation reached 10 stroke volume units. In Exp. 82, Table II, the dog received 20 mg. of tuamine prior to the infusion of 410 c.c. of blood, when cardiac dilatation was also 10 units, but normal circulation was restored.

CARDIODYNAMIC EFFECT OF DRUGS BEFORE AND AFTER HEMORRHAGE

The evidence presented suggests that a drug to be useful in the terminal phase of hemorrhagic shock must have at least the following properties: (1) it must increase cardiac output; (2) it must decrease cardiac dilatation; (3) it must cause a minimal increase in peripheral

resistance; and (4) its action must be of such duration that if an intravenous infusion is begun simultaneously, a quantity of blood sufficient to restore the circulation can be given during the period the drug is acting.

Decrease in diastolic volume is essential because cardiac dilatation has already begun in the terminal phase and the intravenous infusion of blood will of itself tend to increase further the heart size; therefore, the drug selected should be one which would counteract this effect. It must not increase peripheral resistance proportionately more than cardiac output. In the terminal phase there is already increased peripheral resistance and the more this is increased the more difficult it will be for the heart to maintain adequate circulation. By comparing the change in cardiac output with the rise in arterial pressure, the change in peripheral resistance which a drug produces can be estimated. Thus, a drug which causes a large rise in arterial pressure with a minimal change in cardiac output acts primarily on the peripheral vessels, whereas one that causes a smaller rise in arterial pressure and much larger changes in cardiac output must have a primary cardiac action.

With these thoughts in mind a search was made for a quick acting drug which would have a primary cardiac action.

Methyl iso-thiourea.—Methyl iso-thiourea was studied because it had been used by McGeorge, Sherif, and Smirk (1942) in the treatment of traumatic shock in animals. It was injected intravenously into ten normal and five hypotensive dogs (Table VI). The amount given varied from 10 mg. per kilogram to 1.4 mg. per kilogram. In normal dogs the effect on stroke volume was equivocal; it reduced it in five and increased it in the other five. The change varied from a 66 per cent increase to 36 per cent decrease. The heart rate was decreased in all of the normal dogs, the minimum being 7 per cent and the maximum 50 per cent. These changes in stroke volume and rate could not be correlated with the amount of drug given. For example, the same increase in stroke volume and reduction in heart rate was produced by 1.4 mg. per kilogram used in Exp. 55 (Table VI) as had been obtained when 9 mg. per kilogram had been given in Exp. 41 (Table VI).

The cardiac output per minute was decreased in nine of the ten experiments because in all but two (Exp. 36 and 58, Table VI) in which stroke volume increased, the increase was not large enough to compensate for the reduction in heart rate. The reduction in cardiac output also bore no relation to the amount of drug used.

The rise in arterial pressure varied markedly and could not be correlated with the amount of drug administered (Table VI). A handicap limiting its usefulness is the fact that after two or three injections the animal's pressor response is progressively converted to a depressor one.

Methyl iso-thiourea caused an increase in diastolic volume in nine of ten normal dogs. Expressed in stroke volume units, the greatest dila-

TABLE VI

CIRCULATORY DYNAMIC EFFECTS OF METHYL ISO-THIOUREA BEFORE AND AFTER HEMORRHAGE

EXP. NO.	DOG (WEIGHT IN KG.)	DOSE (MG. PER KG.)	STROKE VOL.			HEART RATE			CARDIAC OUTPUT (l. PER MIN.)			ARTERIAL PRESSURE (MM. HG)				CHANGE VENOUS PRESSURE (CM. WATER)	CAR. DIL. (STROKE VOL. UNITS)	C.C. OF BLOOD REMOVED	BLOOD LOSS = PER % B.W.	DURATION OF HYPOTEN. (IN MIN.)
			BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	RISE	% CHANGE					
Before Bleeding																				
36	15	0.10	6.2	10.3	+66	150	110	-27	0.9	1.13	+21	90	132	42	+ 46	+3.5	+2.0			
37	20.3	7.3	25	21	-16	150	140	- 7	3.7	3.0	-21	78	120	42	+ 53	None	+0.4			
38	21.6	7.0	14	11	-21.7	130	120	- 8	1.8	1.3	-28	130	156	26	+ 26	-1.0	+0.35			
40	18.3	8.0	14	15	+ 5	170	140	-18	2.4	2.1	-13	100	132	32	+ 32	+1.0	+1.0			
41	16.7	9.0	15	21	+36	160	80	-50	2.5	1.7	-32	126	208	82	+ 65	+4.5	+1.4			
42	20.3	9.8	16	12	-16	140	150	-22	2.3	1.8	- 6	86	138	52	+ 60	-1.4	-1.0			
55	17.7	1.4	14	19	+35	130	70	-46	1.8	1.36	-26	124	136	12	+ 9	None	+1.07			
56	13.5	7.4	15	10	-33⅓	150	120	33⅓	2.2	1.2	-46	138	202	64	+ 46	+1.9	+0.3			
57	18	2.7	21	17	-20	190	180	- 6	4.0	3	-23	90	138	48	+ 53	+0.5	+0.3			
58	16	3.1	16	19	+22	160	130	-19	2.5	2.5	None	102	130	28	+ 27	None	+0.6			
After Bleeding																				
32	22.5	6.6	8	9	+12	160	140	-12½	1.28	1.26	- 2	48	106	58	+120	None	None	950	4.2	57
35	16.4	9.0	3.5	6.5	+85	130	100	-24	0.36	0.65	+80	40	100	60	+150	None	-2.0	410	2.5	60
37	20.3	7.3	7	9.2	+31	140	120	-15	0.98	1.10	+12	50	78	28	+ 56	None	+1.4	670	3.3	19
38	21.6	7.0	9.0	11.3	+25	160	120	-25	1.4	1.34	- 5	50	90	40	+ 80	+0.2	+0.8	650	3.0	30
40	18.3	8.2	9.0	10.5	+16	170	160	- 6	1.5	1.68	+ 9	54	110	56	+101	-0.3	None	300	1.6	8
42	20.3	9.8	11.7	12	+ 3	150	140	- 7	1.7	1.7	None	54	80	26	+ 48	None	+0.25	400	1.9	13

tation was 2 and the smallest was 0.3. Again it is interesting to note that the smallest dose used (Exp. 55, Table VI) produced as much, or more, cardiac dilatation than occurred in other experiments in which much larger amounts of the drug were given. The effect on venous pressure was not significant.

In the hypotensive dogs, a more uniform dose was given. It varied from 6.6 to 9.8 mg. per kilogram. The stroke volume increased in all, varying widely from +3 to +85 per cent. Heart rate invariably decreased and in three of the five hypotensive dogs the increase in stroke volume was enough to offset the decreased rate with the result that cardiac output increased.

The pressor effect of the drug was comparable to that in normal dogs. The effect on diastolic volume was much less pronounced than had been observed in normal dogs. In only one animal (Exp. 35, Table VI) was heart size reduced. In two there was no change, in two others there was a moderate increase, and in one there was a large increase (1.4 units). Little change in venous pressure occurred.

Mixture of Pitressin and Ephedrine.—A mixture of pitressin and ephedrine has been recommended for use in the treatment of shock by Bourne (1939) and Melville (1932). It was given to five normal dogs and four hypotensive animals (Table VII). In three experiments a dose of $\frac{3}{16}$ gr. of ephedrine and $2\frac{1}{2}$ units of pitressin was used, and in the remaining six experiments $\frac{3}{32}$ gr. of ephedrine and $1\frac{1}{4}$ units of pitressin.

In four of the normal dogs the mixture produced a decrease in stroke volume and in one an increase. Likewise, in four of five dogs heart rate was decreased and in one it was slightly increased. In all of the normal dogs cardiac output per minute was decreased from 20 to 38 per cent in four dogs, and 71 per cent in the fifth.

The mixture had a moderate pressor action averaging 40 mm. Hg. It produced an increase in heart size in four of the five dogs varying from 0.84 stroke volume units to 1.7 units. A definite rise in venous pressure occurred in four of five dogs, the maximum rise being 3.6 cm. of water. The fifth dog (Exp. 39, Table VII) showed no change.

After bleeding, the effect on stroke volume was equivocal. The maximum increase was 50 per cent and the maximum decrease 49 per cent. Heart rate was reduced in three of four dogs. The effect on cardiac output was slight in two experiments, and was decreased in the other two about 50 per cent. The pressor effect was less than it had been in the normotensive dogs. Cardiac size was increased in all the experiments, the amount being definitely more than it had been in the normal dogs. The largest increase was 3.4 units and this occurred after 460 c.c. of blood had been removed (Exp. 42, Table VI), and hypotension had been present forty-five minutes. Venous pressure increased significantly in all of the hypotensive dogs.

TABLE VII

CIRCULATORY DYNAMIC EFFECTS OF A MIXTURE OF PITRESSIN AND EPHEDRINE BEFORE AND AFTER HEMORRHAGE

EXP. NO.	DOG (WT. IN KG.)	DOSE		STROKE VOL.			HEART RATE			CARDIAC OUTPUT (l. PER MIN.)			ARTERIAL PRESSURE (MM. HG)				CHANGE IN VENOUS PRESSURE (CM. OF WATER)	CAR. DIL. (STROKE VOL. UNITS)	C.C. OF BLOOD REMOVED	BLOOD LOSS ≡ PER % B. W.	DURATION OF HYPOTENSION (IN MIN.)
		GR.	UNITS	BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	RISE	% CHANGE					
Before Bleeding																					
39	22	3/16	2½	7.4	6.3	-15	120	110	- 9	0.8	0.6	-22	148	198	50	+33	None	+1.3			
40	18.3	3/32	1¼	8.8	*12.5	+42	170	100	-42	1.5	1.2	-20	132	160	28	+21	+2.0	+1.02			
41	16.7	3/32	1¼	17.6	13.5	-24	140	110	-22	2.38	1.4	-38	114	190	76	+66	+2.0	None			
55	17.7	3/32	1¼	13.6	11.7	-14	130	110	-15	1.76	1.28	-28	122	130	8	+ 6	+3.6	+1.7			
56	13.5	3/32	1¼	19	5	-73	130	140	+ 7	2.4	0.7	-71	118	160	42	+35	+1.7	+0.84			
After Bleeding																					
29	17.4	3/16	2½	6.7	9.0	+50	200	160	-20	1.34	1.4	+ 4	36	54	18	+50	+2.0	+1.5	600	3.4	30
40	18.3	3/32	1¼	9.4	4.8	-49	130	130	None	1.2	0.6	-50	58	76	18	+30	+2.0	+1.7	350	1.9	33
41	16.7	3/32	1¼	4.0	4.9	+25	200	160	-20	0.78	0.78	None	64	84	20	+31	+1.6	+2.2	540	3.2	15
42	20.3	3/16	2½	11	7	-37	140	90	-36	1.5	0.6	-60	56	80	24	+42	+3.6	+3.4	460	2.3	45

TABLE VIII

CIRCULATORY DYNAMIC EFFECTS OF ANGIOTONIN BEFORE AND AFTER HEMORRHAGE AND THE EFFECT OF PAREDRINE IN NORMAL DOGS

EXP. NO.	DOG (WT. IN KG.)	DOSE (C.C.)	STROKE VOL. (C.C. PER MIN.)			HEART RATE PER MIN.			CARDIAC OUTPUT (L. PER MIN.)			ARTERIAL PRESSURE (MM. HG)				CHANGE IN VENOUS PRESSURE (CM. OF WATER)	CAR. DIL. (STROKE VOL. UNITS)	C.C. OF BLOOD REMOVED	BLOOD LOSS = PER % B. W.	DURATION OF HYPOTENSION (IN MIN.)
			BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	RISE	% CHANGE					
Before Bleeding																				
30		5	21	18	-15	150	150	None	3.1	2.7	- 13	100	140	40	+40	None	+0.2			
31	14	5	21	24	+14	170	160	-6	3.4	3.8	+ 11	90	118	28	+31	+0.5	+0.2			
42	20.3	5	26	25.8	- 1.2	160	160	None	4.1	4.01	- 4	70	102	28	+27	+1.0	+0.2			
56	13.5	5	19	14	-27	150	120	-20	2.8	1.6	- 41	114	164	50	+43	+1.3	+0.4			
57	18	4	17	11	-36	160	160	None	2.7	1.7	- 39	98	122	34	+28	None	+0.7			
58	16	3.5	16	14	-15.7	150	130	-14	2.5	1.8	- 38	90	122	28	+31	+0.9	+0.7			
After Bleeding																				
42	20.3	5	8.4	9.6	+13	110	120	+ 9	0.9	1.15	+ 23	52	68	16	+30	+0.7	+1.07	485	2.3	55
56	13.5	5	4	5.2	+30	140	130	- 7.2	0.57	0.68	+ 19	52	98	46	+88	+1.7	+3.7	425	3.1	11
40	18.3	5	9	9.2	+14	160	140		1.4	1.38	- 3.2	58	68	10	+17	+1.0	+1.2	400	2.1	57
Paredrine (1 Per Cent Solution) Before Bleeding																				
57	18	1.0	19	29	+52	160	230	+43	3	6.6	+120	106	160	54	+50	+1.2	-1.05			
58	16	1.0	12.3	19	+54	160	190	+18	1.9	3.6	+ 89	72	120	48	+66	-1.4	-2.68			

Angiotonin.—Six normal dogs received a quantity of angiotonin equivalent in pressor action to 0.5 c.c. of 1:10,000 adrenalin (Table VIII). Stroke volume decreased in five of six dogs; heart rate remained unchanged in three, and decreased in three.

In three hypotensive animals (Table VIII) stroke volume increased, varying from 13 to 30 per cent. Heart rate increased slightly in one and decreased in two. These changes produced concomitant change in cardiac output. The pressor effect was less in the hypotensive dogs than it had been in the normal. A striking effect of angiotonin was that it caused a pronounced increase in diastolic volume when given after bleeding. In Exp. 56 (Table VIII) the increase was 3.7 stroke volume units; in Exp. 42, 1.07 units, and in Exp. 40, 1.2 units (Table VIII). Venous pressure increased in all of the hypotensive dogs. The rise was larger than it had been in the normal dogs.

Paredrine (p-hydroxy-a-methyl phenethylaminehydrobromide).—One cubic centimeter of 1 per cent paredrine was administered to two normal dogs. Stroke volume increased 50 per cent; heart rate increased and the result was a large increase in cardiac output. In both dogs arterial pressure increased almost 50 mm. Hg. The most striking effect produced was a decrease in the diastolic volume. The heart size decreased 1 and 2.6 units. This change in diastolic volume is greater and more prolonged than any previously observed. The effect on venous pressure was equivocal.

Neosynephrin (levo-a-hydroxy-b-methylamino-3-hydroxy ethylbenzene hydrochloride).—Neosynephrin was administered in varying doses to ten normal dogs, and to eight after hypotension (Table IX).

The effect on stroke volume in normal dogs varied widely. In six dogs it increased; the maximum being 39 per cent. In one dog (Exp. 36, Table IX) it was unchanged, and in three it was reduced. The maximum reduction was 27 per cent. These changes bore no relationship to the amount of drug given. Heart rate decreased an average of 16 per cent in nine of the ten dogs and remained unchanged in one. In only one experiment was the increase in stroke volume of sufficient magnitude to compensate for the decrease in heart rate and here (Exp. 35, Table IX) it was increased 16 per cent. The average rise in arterial pressure in normotensive dogs was 46 mm. Hg. Neosynephrin had only a slight effect on diastolic volume in these animals. Heart size was not altered in four and was increased in six dogs. The maximum increase was 1.4 units. Venous pressure increased to a variable extent in seven and was not changed in three.

The drug was administered to eight hypotensive dogs. The amount varied from 0.1 to 0.5 c.c. of 1 per cent solution of neosynephrin. The effect on stroke volume was extremely variable, ranging from an increase of 100 per cent (Exp. 35, Table IX) to a decrease of 30 per

TABLE IX

CIRCULATORY DYNAMIC EFFECTS OF NEOSYNEPHRIN BEFORE AND AFTER HEMORRHAGE

EXP. NO.	DOG (WT. IN KG.)	DRUG (C.C.) 1% SOLUTION	STROKE VOL. (C.C. PER MIN.)			HEART RATE PER MIN.			CARDIAC OUTPUT (l. PER MIN.)			ARTERIAL PRESSURE (MM. HG)				CHANGE VENOUS PRESSURE (CM. OF WATER)	CAR. DIL. (STROKE VOL. UNITS)	C.C. LOSS OF BLOOD	BLOOD LOSS ≡ PER % B. W.	DURATION (IN MIN.)
			BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	% CHANGE	RISE					
Before Bleeding																				
33	22.5	0.1	13.0	11.0	- 16	160	150	- 7	2.0	1.6	- 20	100	114	14	14	None	None			
34		0.1	13.0	14.0	+ 5	160	150	- 7	2.1	2.1	- 1	106	164	58	58	+0.4	+1.4			
35	16.0	0.05	10.2	14.2	+ 39	120	100	-17	1.2	1.4	+ 16	100	164	64	64	+0.6	+0.5			
36	15.0	0.05	12.0	12.0	None	120	100	-17	1.5	1.2	- 20	70	100	42	30	+2.0	+0.6			
38	21.6	0.1	17.0	20.0	+ 17	150	120	-20	2.4	1.6	- 4	130	190	46	60	+3.0	+1.2			
40	11.0	0.07	9.5	9.0	- 6	150	130	-15	1.4	1.1	- 3	128	162	26	34	+1.0	None			
41	16.0	0.07	15.8	20.0	+ 26	140	70	-50	2.2	1.4	- 37	120	192	56	68	+5.7	None			
55	17.0	0.03	18.3	19.6	+ 7	120	120	None	2.19	1.96	- 11	108	146	35	38	None	None			
56	13.5	0.05	17.0	18.0	+ 5	120	110	- 8	2.04	1.98	- 3	118	178	50	60	+0.3	+0.3			
58	16.0	0.05	17.0	12.0	- 27	160	120	-25	2.7	1.5	- 45	100	138	38	38	None	+0.47			
After Bleeding																				
33	22.5	0.1	9.0	9.1	+ 1	80	80	None	0.72	0.72	None	50	72	44	22	+5.0	None	350	1.5	40
35 (I)	16.0	0.05	7.8	8.5	+ 8	100	110	+10	0.78	0.93	+ 19	40	110	150	60		+0.5	300	1.8	10
35 (II)	16.0	0.05	2.5	5.0	+100	100	100	None	0.25	0.50	+100	30	80	166	50	-1.4	-0.6	410	2.5	70
38	21.6	0.1	10.0	7.0	- 30	160	170	+ 6	1.6	1.2	- 20	54	142	162	88	+0.4	+1.0	540	2.5	20
36	16.0	0.05	4.4	4.3	- 3	130	140	+ 7	0.57	0.60	None	44	58	31	14	None	None	300	2.0	1
42	17.0	0.1	11.0	8.0	- 24	160	130	-19	1.7	1.04	None	58	100	72	42	None	None	460	2.2	27
40	13.5	0.07	9.5	8.7	- 9	150	160	+ 6	1.4	1.39	None	52	88	70	36	+0.2	+0.74	350	1.9	29
56	16.0	0.05	4.0	7.1	+ 75	150	160	+ 6	1.13	2.7	+ 88	70	100	52	24	+0.5	+1.2	425	3.1	58

cent in Exp. 38 (Table IX). In Exp. 35 (I) the drug was first injected after 300 c.c. of blood had been withdrawn and hypotension had been present ten minutes. At this time stroke volume increased 8 per cent. A second injection was given to the same dog after a total of 400 c.c. of blood had been withdrawn and hypotension had been present sixty minutes (Exp. 35, II). It produced a 100 per cent increase in stroke volume. At neither time was there any significant change in heart rate. The pressor response after the second dose was 10 mm. Hg less than after the first. Heart size decreased 0.6 units and venous pressure 1.4 cm. of water. In a comparable experiment (Exp. 56, Table IX) in which the neosynephrin was given after 425 c.c. of blood had been removed and hypotension had existed fifty-eight minutes, the stroke volume increased 75 per cent. Contrariwise, in Exp. 36, Table IX, in which the weight of the dog and size of the dose were similar, stroke volume decreased 3 per cent. The average stroke volume during the control period was about equal in Exp. 36 and 56. However, in Exp. 36, hypotension had been present only one minute prior to administration of the drug. The pressor effect was very different in the three experiments. In Exp. 35, a rise of 50 mm. Hg occurred; in Exp. 36 arterial pressure increased 14 mm. Hg, and in Exp. 56 the pressure rose 24 mm. Hg. The change in heart size and venous pressure was different in each of these experiments. In Exp. 35, diastolic volume decreased 0.6 units and in Exp. 56 it increased 1.2 units and was unchanged in Exp. 36.

These results suggest that the effect of neosynephrin on stroke volume may be altered by prolongation of the hypotension but that it does not affect the other circulatory changes.

Adrenalin.—Adrenalin was administered to ten normal and six hypotensive dogs (Table X), the amount varying from 0.2 to 2.0 c.c. of a 1:10,000 solution. In the normal dogs, stroke volume increased in seven animals, an average of 28 per cent, and decreased less than 20 per cent in three. Heart rate was accelerated in nine of the dogs, an average of 19 per cent. Cardiac output increased in eight, an average of 41 per cent; in one dog it was not changed and in another it decreased 40 per cent. Diastolic volume decreased in all of the animals and the average change expressed as stroke volume units was 1.2 units. The average rise in arterial pressure was 32 mm. Hg.

In hypotensive dogs adrenalin was administered before the duration of hypotension was sufficient to cause a decrease in the pressor response. The effect on stroke volume was variable, it decreased slightly in two dogs; in one it was unchanged and in three it increased. Heart rate was increased in four dogs, was unchanged in two, and decreased in another. Cardiac output was increased in all, an average of 16 per cent. The average rise in arterial pressure was 35 mm. Hg. Diastolic volume decreased in five, an average of 1.9 stroke volume units and remained

TABLE X

CIRCULATORY DYNAMIC EFFECTS OF ADRENALIN BEFORE AND AFTER HEMORRHAGE

EXP. NO.	DOG'S WT. (IN KG.)	DOSE (C.C. OF 1:10,000 SOL.)	STROKE VOL.			HEART RATE PER MIN.			CARDIAC OUTPUT (l. PER MIN.)			ARTERIAL PRESSURE (MM. HG)				CHANGE DIASTOLIC VOL. (STROKE VOL. UNITS)	CHANGE IN VENOUS PRESSURE (CM. OF WATER)	C.C. OF BLOOD REMOVED	BLOOD LOSS ≡ PER % B. W.	DURATION OF HYPOTENSION (IN MIN.)
			BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	% CHANGE	BEFORE DRUG	AFTER DRUG	RISE	% CHANGE					
Before Bleeding																				
34	20.0	1.0	14.0	20.0	+40	140	180	+28	2.0	3.6	+81	138	162	24	+ 17	-1.4	-0.6			
35	16.0	0.5	11.0	13.6	+24	110	120	+ 9	1.2	1.6	+33	110	162	52	+ 47	-1.5	None			
37	20.3	0.5	25.0	23.0	- 8	150	170	+13	3.7	3.9	+ 5	80	110	30	+ 37	-1.4	-0.6			
38	21.6	0.5	16.0	23.0	+43	150	170	+13	2.4	4.0	+62	128	162	34	+ 26	-2.1	-0.3			
39	22.0	1.0	12.0	14.0	+16	150	140	- 8	1.8	2.0	+ 3	112	118	6	+ 5	-1.2	-0.6			
40	18.3	0.5	10.0	12.0	+20	170	230	+35	1.7	2.7	+58	78	104	26	+ 33	-1.5	-1.0			
41	16.7	0.5	20.0	16.0	-19	150	180	+20	3.0	3.0	0	108	134	26	24	-1.7	-0.6			
42	20.0	2.0	18.0	24.0	+30	160	170	+ 6	3.0	4.0	+40	86	120	34	40	-0.6	+0.3			
55	17.0	0.3	14.0	13.0	- 8	100	160	+31	2.3	1.4	-40	124	160	40	32	-0.21	None			
56	13.5	0.2	19.0	24.0	+26	140	170	+20	2.6	4.0	+53	118	162	44	37	-0.89	None			
After Bleeding																				
33	22.0	1.0	9.2	8.1	-12	100	140	+40	0.9	1.1	+22	48	80	32	+ 66	-0.6	-0.6	3.0	1.5	24
38	21.6	0.5	10.8	10.0	- 8	170	190	+11	1.8	1.9	+ 4	70	140	70	+100	-1.9	None	450	2.1	8
40	18.3	0.5	8.5	8.5	None	150	180	+20	1.2	1.5	+20	58	88	30	+ 51	-2.3	-1.0	350	1.9	25
41	16.7	1.0	4.2	5.1	+21	170	180	+ 6	0.7	0.9	+31	56	81	25	+ 44	None	-0.3	500	3.0	5
42	20.0	2.0	8.2	10.3	+25	120	120	0	0.9	1.0	+19	48	80	32	+ 68	-0.73	+0.3	485	2.4	2
56	13.5	0.2	4.0	7.0	+75	150	150	0	0.6	0.7	+ 5	50	70	20	40	-1.0	-0.8	425	3.1	60

unchanged in one. The chief difference observed in the action of adrenalin in normotensive dogs and hypotensive dogs was that in the former the average increase in cardiac output was 41 per cent and in the latter 16 per cent. The rise in arterial pressure was about equal in both groups. In both normotensive and hypotensive, diastolic volume was decreased. Changes in venous pressure were variable and were not significant.

Tuamine (2-amino heptane sulfate*).—The cardiac action of tuamine was tested in ten normal and eight hypotensive dogs. The amount given varied from 0.45 to 1.1 mg. per kilogram. In normal dogs it had a varied effect on stroke volume (Table XI). In six dogs it was reduced an average of 31 per cent, in two it increased 57 per cent in one and 19 per cent in the other, and in two it was unchanged. Heart rate increased in five dogs and decreased in five. The maximum increase was 55 per cent and decrease 31 per cent. In six animals cardiac output was decreased, the maximum being 36 per cent; in one it was unchanged, and in three increased, the maximum being 29 per cent.

The pressor effect as compared to the cardiac action was less marked than that of the other substances tested and it could not be correlated with the amount given. In Exp. 56 (Table XI) in which 1.1 mg. per kilogram was administered, arterial pressure increased 12 mm. Hg., while in Exp. 33 with 0.45 mg. per kilogram), the response was 20 mm. Hg. Diastolic volume decreased in seven of the ten normal dogs, the maximum being 1.8 units (Table XI). A small increase occurred in three experiments. Large but variable changes occurred in venous pressure; in four dogs it declined about 2 cm. of water and in three increased 1.0 cm. These changes also bore no relation to size of the dose. In the hypotensive dogs the drug usually produced a striking increase in stroke volume, while in the normal animals it was increased in only two of the ten dogs. The change was proportionately much greater than in normal dogs (Table XI). In Exp. 36 (Table XI), for example, stroke volume increased 140 per cent. The effect of tuamine on heart rate was just as variable in the hypotensive as in normal dogs. However, the consistently large increase in stroke volume was sufficient to compensate for decrease in heart rate in all but one of eight hypotensive dogs resulting in increased cardiac output in seven dogs.

The pressor effect was similar to that observed in normal dogs, and it was significant that in those experiments in which there had been a great increase in stroke volume and cardiac output (Exp. 29, 31, and 32) the pressor response was smaller than in Exp. 42 in which stroke volume decreased, or Exp. 35 in which cardiac output diminished. Diastolic volume was decreased in six of eight hypotensive dogs. This decrease in cardiac size was definite, the maximum being 3.3 units, the

*Eli Lilly and Company.

Table XI

Circulatory Dynamic Effects of Tuamine Sulfate Before and After Hemorrhage

Exp. No.	Dog's Wt. (in Kg.)	Dose of Drug (Mg. per Kg.)	Stroke Vol.			Heart Rate per Min.			Cardiac Output (l. per Min.)			Arterial Pressure (mm. Hg)				Change Diastolic Vol. (Stroke Vol. Units)	Change Venous Pressure (Cm. of Water)	c.c. Blood Removed	Blood Loss = % B. W.	Duration of Hypotension
			Before Drug	After Drug	% Change	Before Drug	After Drug	% Change	Before Drug	After Drug	% Change	Before Drug	After Drug	Rise	% Change					
Before Bleeding																				
32	22.0	0.68	20.0	9.0	- 55	130	200	+53	2.6	1.8	- 30	94	130	36	38	-1.0	+1.0			
33	22.0	0.45	18.0	10.0	- 45	160	180	+12	2.8	1.8	- 36	120	140	20	16	-0.5	+1.2			
34	20.0	0.75	21.0	17.0	- 19	140	170	+21	3.0	3.0	None	116	150	34	29	-0.71	-0.6			
35	16.0	0.93	14.0	11.7	- 17	90	140	+55	1.26	1.6	+ 29	76	120	44	57	-1.0	-2.0			
36	15.0	1.0	10.0	6.0	- 40	120	150	+25	1.2	0.9	- 25	88	104	16	18	-1.8	-2.0			
41	16.7	0.89	15.1	18.0	+ 19	150	110	-22	2.26	2.0	- 12	126	164	38	30	-0.26	+1.0			
55	17.0	0.88	19.0	30.0	+ 57	110	90	-18	2.1	2.7	+ 28	110	138	28	25	+0.15	-1.8			
56	13.5	1.1	17.0	15.0	- 12	150	120	-20	2.5	1.9	- 23	108	122	14	12	+0.17	-2.3			
57	18.0	0.83	12.0	12.0	None	180	150	-17	2.2	1.9	+ 15	138	152	14	10	+0.25	-1.0			
58	16.0	0.93	17.0	17.0	None	160	110	-31	2.7	1.7	- 35	86	112	26	23	-0.41	None			
After Bleeding																				
29	17.0	0.58	4.4	10.0	+127	240	240	None	1.05	2.4	+128	38	44	6	15			600	3.4	11
31	19.0	0.78	7.0	11.0	+ 57	140	170	+21	0.98	1.87	+ 90	38	54	16	42	-1.4	+1.3	450	2.4	29
32	22.0	0.68	6.0	8.0	+ 33	220	220	None	1.3	1.7	+ 33	42	58	16	38	-3.3	+1.0	950	4.2	5
33	22.0	0.45	5.0	5.8	+ 16	140	150	+ 7	0.87	0.93	+ 24	54	66	12	63	-0.8	None	350	1.5	4
35	16.0	0.93	5.3	4.9	- 8	110	140	+27	0.58	0.7	+ 18	50	78	28	56	-3.0	+0.7	360	2.4	35
36	15.0	1.0	4.0	10.0	+140	110	70	-37	0.45	0.7	+ 50	50	80	30	60	-1.2	None	300	2.0	20
42	20.0	1.0	9.0	9.8	+ 8	110	100	-10	1.0	0.98	- 2	58	80	22	37	None	-2.0	460	2.3	41
56	13.5	1.1	6.2	8.3	+ 33	140	130	- 8	0.86	1.07	+ 24	56	92	36	64	-0.5	+1.0	425	3.1	25

minimum 0.5 units. This change could not be correlated with the quantity of tuamine administered. Venous pressure changed variably but in all experiments in which diastolic volume decreased the venous pressure increased.

On the basis of these results tuamine, adrenalin, and paredrine were the only drugs of those tested that possessed the properties which would make them useful in the preinfusion treatment of hemorrhagic shock.

Methyl iso-thiourea was rejected because it did not decrease, but slightly increased, diastolic volume. And the fact that it produced a reduced pressor response or even a depressor one, after a second or third injection, limited its usefulness. The mixture of ephedrine and pitressin was unsatisfactory because it increased diastolic volume. Angiotonin also increased diastolic volume and temporarily reduced cardiac output. Furthermore, the supply of this substance is limited at present. Neosynephrin produced a large rise in arterial pressure and only minor changes in cardiac output, which was indicative of increase in peripheral resistance. In terminal posthemorrhagic shock an increase in the already excessive peripheral resistance might be harmful.

Tuamine decreased diastolic volume to a marked degree in hypotensive animals. The equally consistent increase in cardiac output together with a relatively small rise in arterial pressure suggested that it did not greatly increase peripheral resistance. Paredrine appeared to have the same effect although in two dogs the pressor response was more pronounced than that produced by tuamine. Adrenalin increased cardiac output and decreased diastolic volume, but its action was very brief. Furthermore, it has been established (Kohlstaedt and Page) that the action of adrenalin decreases as the duration of hypotension is prolonged and it would be less effective in the terminal phase of posthemorrhagic hypotension than tuamine or paredrine.

TREATMENT OF TERMINAL POSTHEMORRHAGIC HYPOTENSION BY INFUSION OF BLOOD ALONE

Before undertaking a study of the efficacy of the treatment of severe hemorrhagic shock by administration of a drug prior to the infusion of blood, it was essential that the limitations of the treatment of this degree of shock by the infusion of blood alone should be established. For this purpose five dogs in various grades of severe shock, as determined by the criterion of cardiac dilatation, were treated by infusion of blood alone.

In one animal (Exp. 66, Table I) treatment was started before cardiac dilatation had appeared although the amount of blood removed equalled 4.6 per cent of body weight and hypotension had existed 185 minutes. The intravenous infusion was begun at the rate of 26 c.c. per minute. Venous pressure rose 12 cm. of water and the cardiometer record of diastolic volume rose 53 mm. Stroke volume in-

creased from 4 to 14 c.c. and heart rate decreased from 120 to 60 per minute. Thus, cardiac output was increased from 0.48 liter per minute to 0.84 liter per minute, but arterial pressure increased only 6 mm. Hg during infusion. One hour later circulation was normal, stroke volume having increased to 22 c.c., heart rate to 70, cardiac output to 1.5 liters per minute, and arterial pressure 84 mm. Hg.

In the remaining five experiments of this group (Exp. 62, 63, 69, 89, and 90, Table I) cardiac dilatation was present at the time infusion of blood was begun, and all of the dogs died before it was completed. Arterial pressure had been kept at ±40 mm. Hg during the period of hypotension and was not excessively low when treatment was begun. The lowest was in Exp. 89 (Table I) in which the pressure was 28 mm. Hg. The average increase in the cardiometer record of diastolic volume was 11.6 mm. Intrathoracic venous pressure increased as cardiac dilatation occurred, the minimum being 0.6 cm. of water and the maximum 3.7.

Intravenous infusion caused an increase in stroke volume and a decrease in heart rate in all experiments. Cardiac output increased in three and decreased in two experiments. Arterial pressure did not rise in any of these experiments. Venous pressure increased moderately during infusion. Death occurred suddenly and was preceded by cessation of spontaneous respiration in all experiments. Artificial respiration failed to save the dogs.

TREATMENT OF POSTHEMORRHAGIC HYPOTENSION BY THE ADMINISTRATION OF A DRUG AND INFUSION OF BLOOD

Tuamine.—The preceding experiments demonstrated that circulation could not be restored by intravenous infusion of blood alone if withheld until sufficient cardiac dilatation occurred. Further, it is evident that tuamine sulfate, because of its stimulant action on the heart, might aid in restoration of the circulation, so averting the failure of blood alone. To demonstrate this, ten experiments were performed (Table II) in dogs with severe grades of cardiac dilatation. Tuamine was first injected and quickly followed by intravenous infusion of whole blood. Circulation was restored in all of these animals. The average increase in cardiac output was 30 per cent at the end of the infusion. The infusion produced a temporary rise in venous pressure and diastolic volume, but was less when tuamine was used prior to infusion, than in those treated by blood alone, despite the fact that the rate of administration averaged 40 c.c. per minute, while when blood alone had been given it was only 26 c.c. per minute. In five of the ten experiments in which the combined form of treatment was used, spontaneous breathing had ceased before tuamine was given.

The results of a typical experiment (No. 77) are illustrated in Fig. 2. At *T* (Section *III*) 20 mg. of tuamine were injected and the effects of the drug alone are shown in the remainder of this section. Section *IV* was

taken immediately after the infusion ended. The restoration of stroke volume and arterial pressure are illustrated. Likewise, the rise in venous pressure and diastolic volume produced by the infusion are apparent. Section *V* was taken fifteen minutes later, when cardiac output and arterial pressure were higher than the prehemorrhagic level. Venous pressure and cardiac size had returned to their control level.

Two experiments were performed in which fortuitously the conditions were exceptionally similar and hence serve to illustrate the effect of the combined treatment (Exp. 63 and 75, Fig. 3).

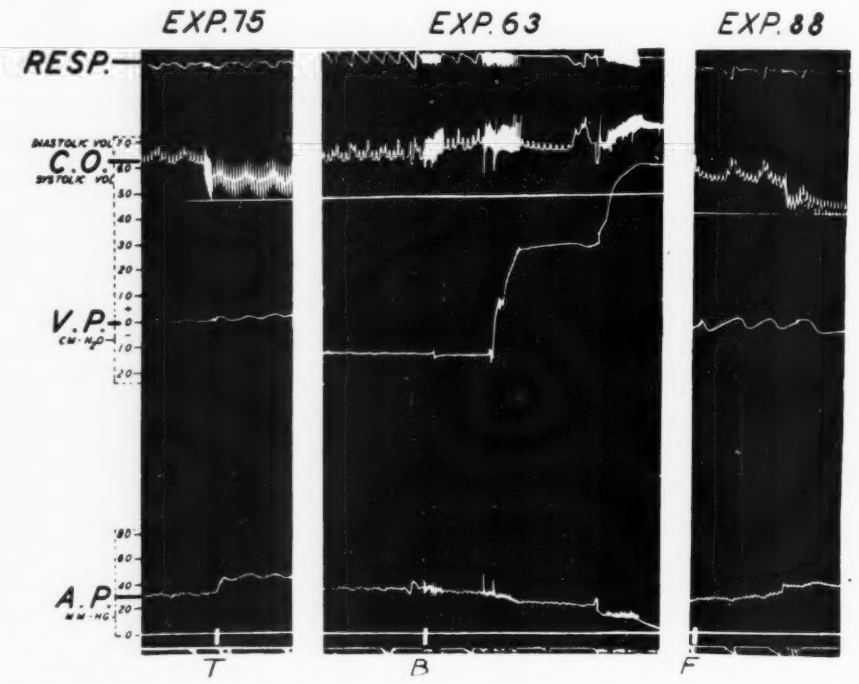

Fig. 3.—Treatment of posthemorrhagic hypotension by drugs and by infusion of blood alone. *Resp.*, Rate and depth of respiration; *CO*, cardiometer record; *VP*, venous pressure, and *AP*, arterial pressure.

Exp. 75, Circulatory effect of tuamine sulfate during phase of cardiac dilatation—*T* 20 mg. tuamine injected; *Exp. 63*, treatment of posthemorrhagic shock during cardiac dilatation by infusion of blood *B* (infusion began); *Exp. 88*, circulatory effect of fouramine during phase of cardiac dilatation; *F* (30 mg. 4-amine injected).

The effect of tuamine on the heart is apparent in Exp. 75 (Fig. 3). Although cardiac output was doubled, the arterial pressure increased only 12 mm. Hg. In Exp. 63 (Fig. 3) in which the status of circulation was similar to that of Exp. 75, the infusion of blood without tuamine had a disastrous effect. Cardiac output decreased from 0.5 to 0.14 liter per minute, arterial pressure declined, venous pressure rose, and the heart dilated. In another experiment the blood was given before the tuamine. The infusion was started when 1.8 stroke volume units of cardiac dilatation were present. After the infusion of 80 c.c. of blood, cardiac dilatation had increased to 2.6 units, and tuamine was admin-

TABLE XII

CONDITIONS DURING HYPOTENSION AND BEFORE TREATMENT

	EXP. 63 DOG'S WEIGHT 11.2 KG.	EXP. 75 DOG'S WEIGHT 11.5 KG.
Systolic dilatation units	2.6	2.4
Blood removed per cent body weight	2.6	2.7
Time in min. required to produce requisite dilatation	105	64
Cardiac output at end of hypotensive period liter per min.	0.5	0.5
Arterial pressure mm. Hg	40	32
Treatment	No tuamine	30 mg. tuamine
Rate of blood infusion c.c. per min.	35	34

istered, but it was ineffective in preventing further cardiac dilatation and ultimate failure.

Fouramine (2-amino-4-methyl hexane sulfate).—Fouramine was administered in four experiments (Exp. 84, 86, 87, and 88, Table III) prior to the infusion. Treatment was not begun until systolic dilatation reached three or more stroke volume units. Thus, the severity of shock in these was equal to, and in some experiments exceeded, that present in the experiments in which tuamine had been used.

The effect of this compound on the circulation is illustrated in Exp. 88, Fig. 3. The changes in stroke volume and systolic volume are striking and are similar to those produced by tuamine. Cardiac output was increased from 0.27 to 0.84 liter per minute but arterial pressure rose only 12 mm. Hg. In three of the four experiments, fouramine and infusion restored circulation to its prehemorrhagic level. In Exp. 87 (Table III), in which five stroke volume units of cardiac dilatation were present, fouramine failed to reduce cardiac size and the dog died during the infusion.

Oneamine (1-amino heptane sulfate).—In two experiments (Nos. 97 and 98, Table III) in which oneamine was substituted for tuamine, the circulation was not restored by infusion of the blood which followed its administration. In Exp. 97 there appeared to be some temporary improvement after the drug was administered but it was of short duration. Within four minutes, arterial pressure had been elevated from 38 to 100 mm. Hg, and cardiac output increased from 0.6 to 1.8 liters. The latter was not maintained and seven minutes later it had decreased to 0.73 liter per minute, although the infusion continued throughout the period. Arterial pressure returned to 46 mm. Hg and the dose of oneamine was repeated. The second injection had no evident effect and the dog died with low blood pressure twelve minutes after infusion was complete.

Oneamine also failed to reduce cardiac size in Exp. 98 (Table III) and cardiac output was decreased rather than increased. The infusion was ineffective.

Paredrine.—One cubic centimeter of 1 per cent paredrine was administered just prior to infusion in two experiments (Exp. 94 and 96, Table III). The injection of paredrine was very effective in reducing heart size in one experiment (No. 94) in which cardiac dilatation was present to the extent of 3.4 stroke volume units. The systolic volume decreased 35 mm. and stroke volume and heart rate increased. Arterial pressure increased immediately from 34 to 90 mm. Hg and when the infusion was ended, the circulation had been restored. But in Exp. 96 (Table III), although the degree of shock was not excessive (1.6 stroke volume units), administration of paredrine did not change the cardiodynamic pattern during the two minutes of the dog's survival. The cardiac action was much slower in its onset than that of tuamine.

Adrenalin.—One dog (Exp. 91, Table III), (1.6 stroke volume units) was treated with 30 gamma of adrenalin just before infusion. During the three minutes the dog survived after it was given and while being infused, no change in cardiac output or arterial pressure occurred. The same dose of adrenalin when administered in the prehemorrhagic period to this dog increased cardiac output from 1.2 to 2.2 liters per minute and elevated arterial pressure 64 mm. Hg.

The loss of responsiveness to adrenalin during prolonged posthemorrhagic hypotension has been described by Rous and Wilson (1919) and by Page (1942). In Exp. 92 (Table III) a large dose (1,000 gamma) was administered when a severe degree of hemorrhagic shock was present (five stroke volume units). The adrenalin increased stroke volume from ±2 to 8 c.c., heart rate from 100 to 180, and thus cardiac output from 0.2 to 1.4 liters per minute. Together with the infusion of blood, adrenalin raised arterial pressure from 28 to 100 mm. Hg. However, the effect was very brief and although the infusion was continued, cardiac output and arterial pressure began to decline after four and one-half minutes. When the infusion ended, cardiac output was 0.63 liter per minute and arterial pressure was 30 mm. Hg. Heart rate and respiration were slow and the dog died one minute later.

From these results it is apparent that the action of adrenalin is too fleeting to be of value in this method of treatment of severe post hemorrhagic shock.

Changes in Roentgenograms of the Heart During Posthemorrhagic Hypotension and Its Treatment.—In the preceding experiments, changes in cardiac size which occurred during hypotension and the period of treatment have been calculated from cardiometer records. As a more direct approach, photographs were taken of the chest with a portable x-ray machine at intervals during experiments in which the cardiodynamic changes were simultaneously being recorded by a cardiometer.

It was important that the position of the dog and the x-ray machine remain constant throughout the experiment; therefore, a special board was constructed which made it possible to slip a cassette under the dog's

back without moving the animal. This was accomplished by constructing a bridge of plywood 2 cm. above the surface of the dog board. Corks were nailed along the board to prevent any lateral motion of the animal.

In all experiments the changes in heart size as estimated from transverse cardiac diameter of the heart shadow were found to parallel those recorded by the cardiometer. These are shown in a typical experiment in Fig. 4. The reduction in size during bleeding and the first part of the hypotensive period were easily discernible, being 1.2 cm. maximum and 0.5 cm. minimum. As hypotension was continued, a progressive increase in cardiac shadow occurred and this appeared simultaneously with the increase in diastolic volume observed in the cardiometer records. Just before treatment was begun, the shadow was slightly larger than during the prehemorrhagic period and much larger than during the first part of the hypotensive period.

The increase in cardiac silhouette above the point of maximum reduction in size, that is, from point *B* (Fig. 1) during the terminal phase of hypotension, varied from +0.8 to +1.5 cm. But change in silhouette, as was to be expected, could not be correlated with stroke volume units. The largest increase did not occur in the experiment with the largest increase in stroke volume units.

Hypotension in these experiments was treated by the injection of fouramine or tuamine and infusion of blood. The cardiac shadow decreased after treatment was completed in four experiments in which circulation was restored, but in one in which treatment failed it continued to increase after the infusion ended.

Tachyphylaxis.—Administration of a single large dose (50 mg.) of oneamine caused the blood pressure to rise 100 mm. Hg or more. A second dose given after the arterial pressure had returned to its initial value elicited little or no rise and a third dose usually caused a fall. Tuamine and fouramine caused no rise and commonly a fall instead. Reversing the order of administration, it was possible to make dogs tachyphylactic by means of tuamine or fouramine to oneamine. Thus, cross tachyphylaxis is produced by a fairly broad group of structurally related amines. It seldom lasts more than an hour.

Pithing the dog, once tachyphylaxis has become established, does not, as is the case with adrenalin, enhance the pressor response.

The pressor action of angiotonin, a peptide, was not blocked by prior tachyphylaxis to these amines.

Treatment of Posthemorrhagic Hypotension in "Intact" Dogs by Administration of Tuamine and Infusion of Blood.—In the preceding experiments application of a cardiometer precluded observations on the survival of the dogs in which the circulation had been restored. Therefore, eight experiments were performed in which the occurrence of cardiac dilatation was determined by the radiographic method. Roentgenograms were taken before bleeding, at intervals during the hypotensive period, and after circulation had been restored by treatment.

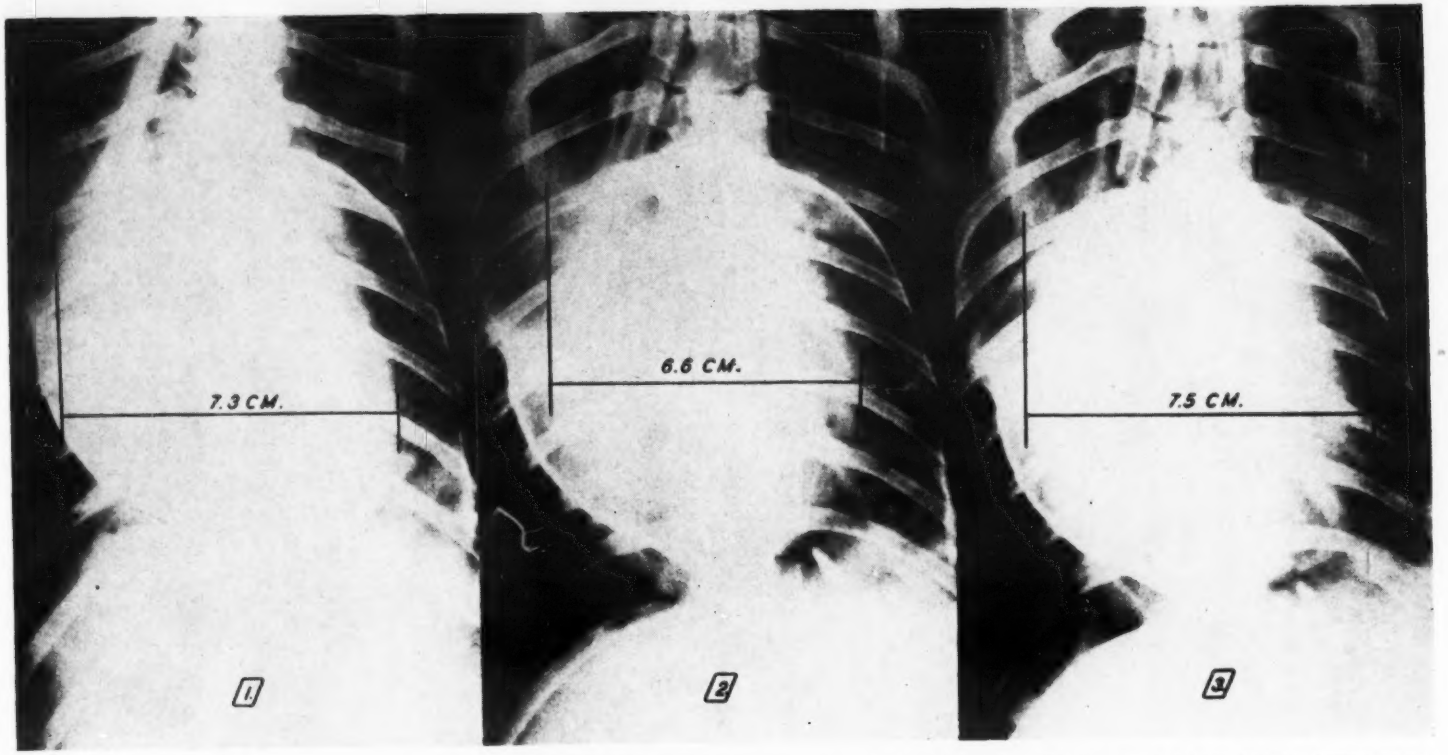

Fig. 4.—X-ray photographs taken before and during prolonged posthemorrhagic hypotension. X-rays were taken during hypotensive period of Exp. 84 (Table III).

(*1*) Photograph of roentgenogram taken during prehemorrhagic period. (*2*) Photograph taken during hypotensive period when cardiometer indicated greatest reduction in cardiac size. (*3*) Photograph taken just before treatment began. Cardiometer indicated an increase of 3.5 stroke volume units in systolic volume.

Arterial pressure was reduced to 40 mm. Hg by intermittent bleeding. Hypotension was maintained at this level until evidence of increase in cardiac silhouette was observed on the x-ray photographs and then it was prolonged until death of the animal appeared imminent because of a sharp decline in arterial pressure or decrease in both rate and depth of respiration.

The cardiac silhouette progressively decreased in size during bleeding in the primary stage of hypotension. The maximum reduction in the transverse diameter of the cardiac shadow was 2.4 cm. and the minimum 1.0 cm. As hypotension was continued the decrease in the cardiac silhouette changed to an increase. The longest period of hypotension which elapsed prior to the appearance of an increase in cardiac shadow was 112 minutes, and the shortest, 60 minutes. In four experiments

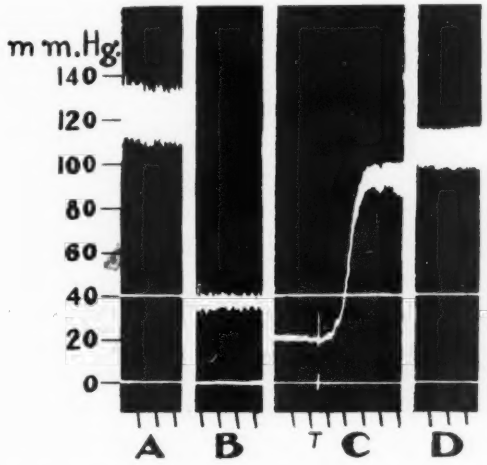

Fig. 5.—Treatment of posthemorrhagic shock by administration of tuamine sulfate, followed by intravenous infusion of blood. Dog's weight: 12.8 kg.
Section *A*, Prehemorrhagic period; Section *B*, after 122 minutes of sustained hypotension produced by removal of 520 c.c. of blood; *Section C*, after 193 minutes of sustained hypotension and radiographic evidence of cardiac dilatation, arterial pressure had declined to 20 mm. Hg, at *T*, 25 mg. tuamine were injected and began intravenous infusion at rate of 50 c.c. per minute; Section *D*, thirty minutes after infusion had been completed, arterial pressure remained within limits of normal.

an intra-arterial injection of 20 to 30 c.c. of blood was necessary to maintain the arterial pressure during the terminal portion of the hypotensive period. This injection of blood temporarily maintained the arterial pressure but did not halt the cardiac dilatation. The average duration of the hypotensive period after the onset of the phase of cardiac dilatation was forty-three minutes. The maximum increase in the transverse diameter over the minimum observed during hypotension of the cardiac silhouette was 0.8 cm., and the minimum, 0.4 cm.

When death appeared imminent, the animals were treated by injecting 2 mg. per kilogram of tuamine sulfate and this was immediately followed by a rapid infusion of blood intravenously. This treatment produced an immediate rise in arterial pressure (Fig. 5). The average

rate of intravenous infusion was 50 c.c. per minute and within three minutes in all experiments arterial pressure was more than 100 mm. Hg. In six dogs this elevation was permanent and the animals recovered. In two the rise was temporary and both dogs died within one hour after the infusion ended. The average arterial pressure at the end of the infusion in the six dogs which recovered was 134 mm. Hg and in these the average arterial pressure twenty-four hours later was 122 mm. Hg. At this time hematocrit and the plasma proteins were normal.

In all experiments the roentgenograms taken as the infusion ended showed an increase in the size of the cardiac silhouette. The heart shadow was now larger than it had been in the prehemorrhagic period. In the six dogs which recovered after infusion was completed and circulation stabilized, the cardiac silhouette gradually decreased so that in the pictures which were taken thirty to sixty minutes after infusion it was smaller than it had been in the prehemorrhagic period. In the two dogs in which treatment failed, the cardiac shadow in the roentgenograms taken after treatment did not decrease but continued to increase as arterial pressure declined.

DISCUSSION

One of the chief objections to the use of a cardiometer in the study of circulatory dynamics has been that conditions of the experiments were very abnormal since the normal pressure relations in the thorax were disturbed. This objection has been overcome in our experiments by closing the opening in the pleura and restoring negative pressure. The importance of this maneuver has been demonstrated by Boyd and Patras (1941). The fact that the venous arterial pressures and circulation time were the same after the cardiometer was applied as before is evidence that it did not interfere with cardiac function.

The changes in circulatory dynamics during posthemorrhagic shock obtained under conditions of these experiments were similar to those observed by Abell and Page (1942) in the blood vessels of cats' mesenteries and rabbits' ears. They found by direct microscopic observation that the arterioles and arteries were constricted by active muscular contraction after severe hemorrhage and that relaxation of these vessels occurred in the terminal stages of shock. The reduction in cardiac size during the first phase of hypotension is comparable to the stage of vasoconstriction, while dilatation of the heart is associated with the stage of relaxation of the arterioles. This similarity of behavior of peripheral vessels and the heart is to be expected if we remember that the heart is only a specialized portion of the vascular system.

The progressive nature of the changes in circulatory dynamics which occur as posthemorrhagic hypotension is continued have been demonstrated. During the period of bleeding, there was a rapid decline in stroke volume and cardiac output, but the change in pulse rate was variable. The need to modify the concept that pulse rate varies in-

versely with fall in blood pressure and cardiac output has already been pointed out in clinical studies by McMichael (1944). After arterial pressure had been fixed at a hypotensive level and no more blood was withdrawn, cardiac output and heart size continued to decrease as hypotension was further prolonged. Definite changes appeared in the cardiodynamic pattern. Diastolic and systolic volume began to *increase* rather than decrease. Stroke volume continued to decrease and the heart rate grew slower. These changes resulted in a further decline in the already reduced cardiac output. Venous pressure rose concurrently with the rise in heart size, but arterial pressure remained constant for some time after the onset of dilatation, to be followed by a decline and death. Arterial pressure could be maintained for a long time by intermittent intra-arterial injections of 35 to 50 c.c. portions of blood, but this did not decrease the rate of cardiac dilatation.

The rate at which cardiac dilatation occurred in the terminal phase of shock varied considerably. In those animals in which it occurred rapidly a greater degree of dilatation was tolerated than when the rate was slower. In five dogs in which respiration ceased before treatment started, the time between the onset of cardiac dilatation and cessation of respiration varied from seven to forty-four minutes. The demonstration by roentgenographic study of an increase in traverse cardiac diameter with an increase in cardiac size, as indicated by the cardiometer, is evidence that the cardiac volume changes recorded were not artifacts.

The changes in circulation time occurring in the early stages of posthemorrhagic shock indicate that vasoconstriction and reduction in size of the heart are beneficial adaptations, for circulation time is shortened after having been prolonged by bleeding. As hypotension continues and cardiac dilatation occurs, it again lengthens.

We wished to produce a degree of posthemorrhagic shock which could not be satisfactorily treated by the infusion of blood alone, and therefore, it was essential that a satisfactory criterion be established for this degree of shock before undertaking a study of therapy. Many experiments were carried out in which various criteria such as the duration of hypotension, amount of blood removed, and the level of arterial pressure were used, but they all proved to be inadequate for our purpose. Even loss of responsiveness to adrenalin or reduction of stroke volume proved unsatisfactory because some dogs could be successfully treated by the infusion of blood alone when the requirements of these criteria had been fulfilled.

We observed that if hypotension had been continued until cardiac dilatation appeared, then treatment by blood alone failed. Five control experiments were carried out in which hypotension was continued until the stage of cardiac dilatation was present and then the infusion of blood started. Treatment by this method failed in all five experi-

ments. Administration of blood seemed to hasten cardiac failure rather than overcome it. If the rate of infusion was reduced sufficiently so that cardiac dilatation did not increase, then it was so slow that the animal died before it could be completed. Having shown that shock of great severity could be produced and also the intensity of it measured to a degree, we attempted to augment the treatment by blood infusion with drugs.

From our observations of the circulatory changes produced by prolonged posthemorrhagic hypotension, it seemed probable that the most important action of such a drug would be to augment the output and force of the heart. If the cardiodynamic pattern could be changed from one of progressive dilatation to constriction and increased output, then infusion of the blood would not have the deleterious action that it does. Of the drugs studied in normal and hypotensive animals, tuamine, paredrine, and adrenalin produced the desired change. Of these, tuamine appeared the most satisfactory because not only did it increase stroke volume but it decreased the diastolic volume. Since, in comparison with adrenalin and paredrine, it caused a proportionately greater increase in cardiac output than in arterial pressure, it seemed less active as a peripheral vasoconstrictor. Wiggers and Middleton (1944) have demonstrated that peripheral resistance increases as cardiac output declines in early hemorrhagic shock, and therefore, if a drug increases peripheral resistance at this time, it would be harmful rather than beneficial. In the late stage of shock, when the heart fails and arterioles are partially dilated, still the imposition of vasoconstriction will intensify rather than lessen the basic defect, the insufficiency of tissue perfusion. Such insufficiency of perfusion, with resultant anoxia and metabolic change, determines the character of shock and, while the larger emphasis of this report is laid on the participation of the heart in causing it, we do not overlook the significance of concurrent changes in other parts of the vascular system, nor in other systems than the circulatory.

Recently we have had an opportunity to observe the effect of increased cardiac output and low arterial pressure in a patient in whom this condition had been brought about by a large dose of arsenic trioxide (Page, Taylor, Kohlstaedt, 1943). In this patient cardiac output was 5.3 liters and arterial pressure by direct measurement 30 mm. Hg, which resulted in a calculated peripheral resistance of 17 (normal 100). The patient was cooperative, able to move about at will, and suffered no deleterious effect from the hypotension, except urinary suppression. This observation emphasized to us that better tissue perfusion is desirable in the treatment of shock rather than elevation of arterial pressure. Tuamine appeared to be a substance which caused improvement in cardiac output with the least rise in arterial pressure and the smallest change in peripheral resistance.

We did not expect tuamine alone to restore circulation to its prehemorrhagic level, but only to produce sufficient improvement so that intravenous infusion of blood would be effective and possible once cardiac dilatation had occurred. This proved to be true. Stroke volume and cardiac output were restored in all the dogs by the combined method of treatment, whereas when treated by blood alone, stroke volume increased in some dogs temporarily but cardiac output was not increased. The heart rate decreased rapidly in those experiments in which stroke volume was increased. The rate of rise in arterial pressure in the dogs which received tuamine and blood closely simulated that produced by intra-arterial infusion in less severely shocked animals (Kohlstaedt and Page, 1943).

Oneamine was not as effective as tuamine because its action was of shorter duration. Fouramine seemed about as effective as tuamine. Paredrine had somewhat similar circulatory dynamic action, but it was considered less suitable because of the slow onset of its action and because it did not stimulate respiration to the same extent as tuamine. Adrenalin was of little value because of its very short action; a small dose was ineffective and a large dose produced a sharp increase in peripheral resistance and proportionately less increase in cardiac output. Therefore, it might even be harmful because of further increase in peripheral resistance without concomitant increase in cardiac output.

Oneamine, tuamine, and fouramine all produced crossed tachyphylaxis, usually after the second large dose, a tachyphylaxis apparently limited to amines of similar structure because angiotonin, a peptide, was unaffected in its pressor response in the face of established amine tachyphylaxis. The refractory period lasts about one hour in dogs. Unlike adrenalin, pithing does not enhance the response to these amines.

Having shown that circulation could be satisfactorily restored with the cardiometer in place, it seemed desirable to perform experiments in which survival could be studied and yet use a criterion of the severity of shock similar to the one established using the cardiometer. Measuring the transverse cardiac diameter by means of the x-ray proved quite satisfactory. Six of eight dogs treated by the combined method made complete recoveries after having reached the stage of cardiac dilatation.

In these experiments a longer period of hypotension elapsed in every instance before cardiac dilatation was detected by the radiographic method than had elapsed before it was shown by the cardiometer. This is due to the fact that the cardiometer is able to detect smaller changes in cardiac size, and possibly also that the application of the cardiometer added to the severity of the shock. An effort was made in these eight experiments to prolong hypotension as long as possible to achieve the greatest amount of cardiac dilatation before treatment was instituted. The very rapid rise in arterial pressure produced by the combined method of treatment was comparable to that observed in the dogs in which less severe posthemorrhagic shock had been treated by intra-

arterial infusion of blood (Kohlstaedt and Page, 1943). Definite improvement in depth and rate of respirations was produced by tuamine in these dogs.

A matter of importance in terminal hemorrhagic shock is the rate at which blood is infused. If it is too rapid, further dilatation of the heart occurs and death is hastened. If, on the other hand, it is too slow the progressive failure of the circulation continues almost unchecked and the animal succumbs before an adequate amount of blood is made available. It was a striking observation, therefore, that when the infusion of blood was preceded by the administration of tuamine, much greater rates of infusion were tolerated than without the drug. The rate was almost comparable to that when the intra-arterial method of infusion is employed, a very rapid rate indeed in some cases.

SUMMARY

1. Studies on the circulation of anesthetized dogs were made before and after prolonged hemorrhagic hypotension by records of stroke volume and cardiac size with the closed chest type of cardiometer (Boyd) of intrathoracic venous pressure, circulation time (NaCN method), arterial pressure, and respiration. The effects of methyl iso-thiourea, angiotonin, paredrine, neosynephrin, adrenalin, mixtures of ephedrin and pitressin, and the amines, oneamine (1-amino heptane sulfate), tuamine (2-amino heptane sulfate), and fouramine (2-amino-4-methyl hexane sulfate), were observed before and after hemorrhage in a search for a substance which would aid in restoring the circulation once it had seriously failed. Other experiments were carried out in which the cardiometer was not used, but the changes in heart size were estimated from x-ray photographs, so allowing survival of the animals to be studied.

2. Hemorrhage caused immediate reduction in stroke volume, diastolic volume, and venous and arterial pressure, followed by a rise in venous and arterial pressure, but maintenance of the reduced stroke volume and diastolic volume. After a prolonged period of hypotension, venous pressure rose sharply and this was followed by progressive increase in heart size despite further bleeding. Since systolic volume increased more rapidly than diastolic, stroke volume grew smaller as dilatation progressed and cardiac output was further decreased by bradycardia. In this terminal period when the size of the heart was increasing, administration of plasma usually precipitated circulatory collapse and death.

3. Methods for the recognition of the terminal (''irreversible'') phase of shock were studied and all found wanting except for one. This was the determination of the relative amount of cardiac dilatation. A ''stroke volume'' unit was ascertained by measuring the height of the cardiometer tracing at that point when cardiac dilatation could first be

detected. When the systolic volume had risen to a point equal to the height of the stroke volume, one unit of dilatation had occurred; almost no animals survived despite attempts to reinfuse blood.

4. Among the various drugs tested on both normotensive and hypotensive animals, tuamine was selected chiefly because of its quick stimulating action on the heart without significant peripheral vasoconstrictor action.

5. Tuamine, like oneamine and fouramine, causes crossed tachyphylaxis limited to structurally related amines but not extending to peptides such as angiotonin. These amines differ from adrenalin in that destruction of the nervous system does not enhance their pressor action.

6. Injection of tuamine immediately followed by infusion of blood allowed the blood to be given at a fast rate. The combined treatment caused a sharp rise in arterial pressure, usually to normal, which in most cases was sustained.

Experiments in which survival was sought were performed without the use of the cardiometer but by determining cardiac dilatation by means of x-ray photographs. Most of these animals recovered when given the combined treatment despite the very severe conditions imposed.

We wish to express our grateful appreciation to Mr. Clifford Wilson for his assistance.

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Review of Recent Meetings

MEETING OF THE AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS AT STOCKBRIDGE, MASS. JUNE 8 TO 10, 1944

C. D. Creevy, M.D., Minneapolis, Minn.

Wednesday, June 8

A CASE reported by **M. F. Campbell,** New York, described a varicocele in a boy of 12 years. It proved to be due to compression of the spermatic vein by aberrant renal vessels. Cure followed division of the aberrant vessels and of the spermatic vein.

His second case report concerned a premature infant with retention of urine apparently due to a birth injury to the nervous system. Recovery followed prolonged use of an inlying catheter.

Charles M. McKenna of Chicago described two cases of true lateral hermaphroditism with hypospadias. In each instance what was thought to be an undescended left testis proved to be an ovary. The presence of a testicle on the right side was proved by biopsy. They were treated by left oophorectomy, straightening of the penis, and urethroplasty.

C. M. Davis, Philadelphia, has evolved rather a complicated method of treating midscrotal hypospadias. Because of the location of the external urinary meatus it is, in his opinion, impractical to divert the urine during healing of the urethroplasty, by means of the usual perineal urethrostomy. After preliminary straightening of the penis, he constructs the glandular urethra from the foreskin, and the penile urethra by the method of Duplay. However, the Duplay plastic is continued behind the external meatus to the posterior edge of the scrotum, and a catheter is inserted through this accessory canal into the bladder. When healing is complete, the accessory canal is excised.

C. L. Deming, New Haven, treated a patient for papillomatosis of the urethra and carcinoma of the bladder by repeated fulguration of the urethra, excision of the carcinoma of the bladder, and finally by removal of the penile urethra because of recurrence. Twelve years after the first treatment, one lung was removed because of metastases. One year later, however, there was evidence of metastasis in the ilium.

H. J. Jewett, Baltimore, has done twenty-five ureteroenterostomies and total cystectomies for carcinoma of the bladder. Having observed that a stony induration of the outer surface of the bladder ordinarily meant early recurrence and death, he reviewed the protocols of 107 autopsies in vesical carcinoma, and found no metastases when the growth was confined to the mucosa and submucosa, a few when there was but little invasion of the muscularis, and many (52 of 89) when the outer coats of the bladder were invaded. Bimanual palpation of the bladder under anesthesia is of great value in detecting the penetration of the wall of the bladder which means that cure by any method is very unlikely.

A. J. Scholl of Los Angeles had a patient with a vesical diverticulum containing a papillary carcinoma as well as an xanthoma which extended out of the

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diverticulum onto the adjoining vesical mucosa. The patient was well one year after excision of the lesions. Scholl cited the occurrence of the xanthoma in the bladder as a curiosity.

R. C. Graves of Boston has done ureteroenterostomy and total cystectomy for vesical carcinoma a number of times since 1933. He transplants one ureter at the first stage, and at the second transplants the other ureter and removes the bladder. He employs continuous spinal anesthesia with great satisfaction. One patient is well 10½ years after operation and has a normal excretory urogram.

In the discussion **G. G. Smith,** Boston, reported ten cystectomies in the past year with but one death. **Quinby** of Boston and **Colby** emphasized their view that external irradiation should not be employed in any tumor of the bladder which is amenable to operation.

F. H. Colby of Boston discussed an unusual syndrome called Reiter's disease, characterized by conjunctivitis, polyarthritis, prostatitis, and urethritis. In his three cases, smears and cultures of discharge from the eyes, joint fluid, urethral discharge, prostatic secretion, and urine were negative, and chemotherapy, including penicillin, was of no avail. The cause of the disease is unknown. All patients recovered.

G. R. Livermore, Memphis, treats urethral strictures by means of a bougie carrying a laterally placed strip of copper. Under local anesthesia, current from a surgical diathermy machine is passed through a strictured area. The current used is not strong enough to cut but is intended to cause shrinkage of the tissue. Periodic dilatations are continued. Livermore believes that the method facilitates dilatation and delays recontraction. It may be used more than once in a given case.

J. A. Taylor, New York, had a patient who had had excisions of epithelial horns of the glans penis on five different occasions. He has been free of recurrence for a year or so, but Taylor anticipates more recurrences.

In the discussion, **Huggins** called attention to the similarity between this lesion and the papillomas of the penis occurring in a certain strain of wild rabbit. The lesion in the rabbit is transmissible, and is thought to be due to a filtrable virus.

Friday, June 9

G. S. Foulds, Toronto, described a case of renal calculus due to an adenoma of the parathyroid, which was removed.

H. G. Hamer and **H. O. Mertz** of Indianapolis were able to dissolve a recurrent renal calculus (two previous operations) composed of alkaline earths by prolonged irrigation with the "solution G" of Suby and Allbright.

H. G. Bugbee of New York, who was awarded the Keyes medal for achievement in urology, described a technique for nephrolithotomy for branched renal stones in which Gerota's (perirenal) fascia is left attached to the kidney. This fibrous layer, thickened by the previous operation, serves to hold the mattress sutures with which the nephrotomy is closed around a nephrostomy tube.

H. C. Bumpus of Pasadena did a left nephroureterectomy for a pyonephrosis due to ureteral calculi in a hypoplastic kidney in a 27-year-old male with severe hypertension. The systolic pressure dropped from 220 to 150, but a few days later paroxysmal dyspnea and hypertension appeared, and the patient died on the fourteenth postoperative day in uremia. At autopsy the artery to the remaining kidney contained a thrombus. The essayist believed that the sequence of events indicated that the hypertension was renal in origin, coming originally from the left kidney and, when thrombosis and infarction developed after the left nephrectomy, from the right.

W. F. Braasch, Rochester, Minn., reviewed the various unilateral renal lesions which may cause hypertension. He was unable, in a study of a large series of

patients with nephroptosis, to uncover evidence indicating any relationship between renal ptosis and hypertension.

In the discussion of the papers, **Barney** and **Colby** of Boston and **Keyser** of Roanoke pointed out that many stones have organic matrices or nuclei which are insoluble in solution G, and that very compact calculi are themselves insoluble. Keyser suggested that a ½ per cent solution of urease might effect a dissolution of the organic material in some cases. **Colston** (Baltimore) dissolved a recurrent calculus by long-continued irrigations with solution G through a nephrostomy.

Scholl, also in the discussion, reported several cases of hypertension in which bilateral narrowing of the aortic orifices of the renal artery was found at necropsy. **Nesbit,** Ann Arbor, had no success with nephrectomy for hypertension in renal hypoplasia.

J. C. McClelland, Toronto, succeeded in excising a papillary carcinoma of the pelvic ureter and making an end-to-end anastomosis. It was done quite recently.

A. I. Dodson of Richmond, Va., described what he thought to be a large diverticulum, containing a stone, in the pelvic ureter of a woman. It was treated by local excision and nephrectomy. Since there was a duplication of the left renal pelvis, the reviewer ventures to suggest that this was an instance of an ectopic ureteral orifice ending in a cyst of Gaertner's duct.

V. J. Oconor, Chicago, presented a case in which pain in the left flank had been present for fifty years. The patient proved to have a diverticulum of the right wall of the bladder, a large stone in the left ureter, a left hydronephrosis containing 4,800 c.c. of urine, and a benign hypertrophy of the prostate. Treatment, which was successful, included vesical diverticulectomy, cystostomy, ureterolithotomy and ureterostomy (one stage), transurethral resection, and nephroureterectomy.

J. D. Barney, Boston, gave a follow-up report upon a patient who had a nephrectomy for adenocarcinoma in 1932, and a pulmonary lobectomy for metastases in 1933, and who was living and well in 1944. Such solitary metastases are exceedingly rare.

N. J. Heckel of Chicago excised a mass from the spermatic cord and found it to be a tuberculoma. He could find only two cases in the literature. In the discussion **Barney** reported a similar case, the patient well twenty-five years after excision of the mass and corresponding testicle.

B. S. Barringer, New York, reviewed a considerable series of testicular neoplasms. Eighty per cent were classified as seminomas, and 17 per cent as adenocarcinomas. They were treated by orchidectomy and external irradiation. Thirty per cent of the patients were well five years after treatment, including several who had abdominal metastases when treatment was started.

W. H. Toulson, Baltimore, treated a young negro man with elephantiasis of the penis and scrotum due to lymphogranuloma, by simple excision and skin grafting with a good end result.

Saturday, June 10

Charles Huggins of Chicago discussed an enzyme found in the normal prostatic secretion and capable of liquefying clotted blood or semen. It is a globulin, and is present in increased amounts in long-standing prostatitis.

N. P. Rathbun of Brooklyn reviewed the results of castration in twenty-three cases of carcinoma of the prostate done in the last three years. Only two were not benefited. There was, however, nothing resembling a cure.

R. M. Nesbit, Ann Arbor, compared the results which followed treatment of carcinoma of the prostate by castration (seventy-five cases) with those which resulted from the administration of estrogens, usually 1 mg. of stilbestrol daily (fifty cases). The two methods were about equally effective in relieving pain and in

increasing body weight. Castration was superior to therapy with estrogens in producing amelioration of obstruction to urination, shrinkage of the primary lesion, and regression of metastases. He called attention to a case in which an elevated serum acid phosphatase fell to normal after treatment and remained so until death although, at autopsy, the primary and metastatic lesions contained an abundance of acid phosphatase (special stains).

In the discussion, **Herbst** of Washington stated that some of his patients had developed avitaminosis while taking estrogens. He believed that the administration of thiamine and nicotinic acid had increased comfort and prolonged life in some of them. He advocates increased doses of estrogens when smaller ones fail, and castration if the larger ones are ineffective.

Davis of Philadelphia cited two cases of mania following the administration of estrogens.

Dean, New York, disagreed with Nesbit, stating that the reduction in the size of the primary tumor was greater with estrogens than with castration. Sixty per cent of his patients had relapses six to eight months after castration; he felt that those treated with stilbestrol remained comfortable longer, and that the greatest relief was seen in those patients with striking hypertrophy of the breasts.

Huggins, Chicago, has some patients who are clinically well four years and nine months after castration; bony metastases have disappeared completely on x-ray in five of eighty castrated patients. In his experience a failure after castration is not amenable to therapy with the estrogens, and vice versa. Nesbit disagreed with this view.

A. L. Dean of New York described the case of a young woman who had received heavy irradiation of the left abdominal area for what was clinically a lymphosarcoma. The mass disappeared, but 7½ years later she had a hypertension of 180/100. She proved to have a contracted left kidney with reduced excretion of diodrast and mannitol, but a normal differential phthalein. The left kidney was removed, and showed shrinkage of the lower half with advanced arteriosclerosis. The blood pressure has remained normal during the ensuing fourteen months.

E. G. Crabtree of Boston discussed a patient who had a leiomyoma of the kidney containing a hemorrhagic cyst, and who was well many years later.

A. R. Stevens, New York, described two cases in which polycystic kidneys were recognized years before death, and in which repeated cortical infections were relieved periodically by surgical procedures and by urinary antiseptics, but which finally caused death.

Robin Pearse, Toronto, discussed the acid-base equilibrium in urological patients, particularly those with prostatism. He emphasized the importance of discovering and correcting acidosis, usually by the administration of 5 per cent sodium bicarbonate intravenously.

Emerson Smith, Montreal, had several patients with essential hematuria, in whom the prothrombin time was prolonged, and whose bleeding ceased after the administration of vitamin K. He also advocated the use of dicumarol in hematuria with repeated urinary retention from clots when the causative lesion was inoperable, as in far advanced renal and vesical neoplasms, simply to prevent clotting in the bladder and to increase comfort. He had done this successfully in three cases.

Leon Herman and **L. B. Greene** of Philadelphia discussed diverticula of the female urethra and reported six cases. Simple excision is usually curative.

THE TWENTY-SIXTH ANNUAL MEETING OF THE AMERICAN BRONCHO-ESOPHAGOLOGICAL ASSOCIATION

PAUL H. HOLINGER, M.D., CHICAGO, ILL.

THE twenty-sixth annual meeting of the American Broncho-esophagological Association was held June 6, 1944, in New York. The following papers were presented:

Robert L. Moorhead, Brooklyn, N. Y., presided. In his presidential address Moorhead mentioned the advances in the field of bronchology and esophagology which had taken place during the years in which the Association had held its meetings. He also discussed the future of bronchoscopy, stressing the role which chemotherapy applied bronchoscopically will play. Finally, Moorhead mentioned the limitations of bronchoscopy as a diagnostic aid. One example is the inability to obtain more than 75 to 80 per cent positive biopsies in suspected bronchogenic carcinoma. He suggested one means of improving this figure through the use of bronchoscopically directed needle biopsy.

Gabriel Tucker and **Joseph P. Atkins** (by invitation), Philadelphia, Pa.: **Recent Trends in the Bronchologic Use of Chemotherapeutic and Biotherapeutic Agents.**—These authors summarize their experience with the endobronchial and systemic administration of chemo- and biotherapeutic agents which may be applicable to various bronchopulmonary diseases. Autogenous vaccines were found to be useful adjuncts to the treatment of chronic tracheobronchitis and allergic tracheobronchitis. Epinephrine, administered ten minutes before bronchoscopy, was considered of value as an aid to bronchoscopic aspiration of secretions from asthmatic patients. They state that of the many drugs which have been applied locally in the bronchi for the treatment of infection, the sulfonamides and penicillin are the first which are both noninjurious to the lung and possess therapeutic effectiveness. The sulfonamides are introduced into the bronchi with a powder blower, macrocrystalline sulfanilamide and microcrystalline sulfathiazole being used. Penicillin used locally in the tracheobronchial tree was introduced in aqueous solution.

Porter P. Vinson, Richmond, Va.: **Treatment of Chronic Nontuberculous Pulmonary Infection by Bronchoscopy and Insufflation of Sulfonamide Compounds.**—Vinson states that since 1938 he has treated approximately 100 patients with chronic suppurative pulmonary disease other than abscess, by bronchoscopic aspiration followed by the intrabronchial insufflation of powdered sulfonamide preparations. He uses a mixture of two parts of sulfanilamide and one part of sulfathiazole. He stated that one-half of the patients thus treated had been benefited. No untoward results were observed in any of the patients. Improvement varied from almost complete relief of symptoms in patients with chronic asthmatic bronchitis associated with purulent secretion, to about 75 per cent reduction in cough and expectoration in patients with well-established bronchiectasis.

The papers of **Tucker** and **Atkins**, and **Vinson** were discussed together since their contents dealt with the same subject. **William Lell**, Philadelphia, demonstrated the manner in which the blood levels of the sulfonamide compounds varied with bronchial insufflation. **Louis Clerf**, Philadelphia, pointed out the fact that in the presence of pus the bacteriostatic action of the sulfonamide compounds is inhibited. Thus, the efficacy of their introduction into the purulent bronchiectatic areas was open to certain theoretical questions.

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CASE REPORTS

James A. Downing, Des Moines, Iowa: **Unsuspected Safety Pin Penetrating the Posterior Mediastinum.**—Two case reports of safety pins perforating the esophagus and lodging in the posterior mediastinum were presented. In neither case could the history of the time of ingestion of the foreign body be obtained. The first infant, 18 months of age, had been seen by a physician because of difficulty in breathing. A bilateral pnemothorax was found with the safety pin in the posterior mediastinum. Chest aspiration and supportive measures were unsuccessful and the child died thirty-six hours following admission to the hospital. The second infant, 10 months of age, was also seen by a physician because of difficulty in breathing. X-ray pictures revealed a perforation of the esophagus and trachea by an open safety pin. The infant recovered following removal of the foreign body. These cases were presented because in neither case was the history of foreign body elicited, the parents consulting the physician because of respiratory difficulty.

W. Likely Simpson, Memphis, Tenn.: **Mediastinal Complications Associated With Esophagoscopy.**—Two cases of mediastinal abscess were presented. In the first case an esophagoscopy was followed by a mediastinal abscess in a patient with a carcinoma of the esophagus. In the second case mediastinitis followed an esophagoscopy which was done to remove a chicken bone. A mediastinotomy was performed for drainage of the posterior mediastinum and the patient eventually recovered.

Clyde A. Heatly, Rochester, N. Y.: **Perforation of the Lower Esophagus: Recovery With Chemotherapy and Gastrostomy.**—In this case mediastinal and subcutaneous emphysema with pleural and pneumonic changes at both lung bases followed an apparently uneventful esophagoscopy under general anesthesia. The procedure was performed for dilatation of a mild cardiospasm by means of a pneumatic bougie. This patient recovered. Treatment consisted of withholding all fluids and food by mouth, establishment and maintenance of a blood level of sulfadiazine of about 22 mg. per cent six days with subsequent gradual reduction and withdrawal on the twelfth postoperative day, and a gastrostomy which was continued for about three weeks. In conjunction with the mediastinal and subcutaneous emphysema, the patient developed a white blood cell count of 48,000 twenty-four hours following the perforation.

William A. Lell, Philadelphia, Pa.: **Safety Pin in the Esophagus With Perforation of the Pericardium.**—Lell presented a case of a 10-month-old infant suspected of having pneumona, who was found on x-ray examination to have a safety pin in the lower esophagus. The cardiac shadow was markedly enlarged. Following removal of the safety pin, 30 c.c., and subsequently 15 c.c. more of purulent material were aspirated from the pericardium. Chemotherapy and transfusions were used. After a stormy convalescence the child made a complete recovery.

Thomas Carmody, Denver, Colo.: **Removal of Denture From Upper End of Esophagus.**—A large denture with several clasps impacted in the upper esophagus was extracted.

John H. Foster, Houston, Texas: **Impacted Foreign Body in the Esophagus Requiring External Removal.**—A 5-year-old boy who had swallowed a marble developed extreme difficulty in breathing. His mother attempted to remove the foreign body digitally, and this resulted in forcing the foreign body further down into the esophagus, from which attempts to remove it either upward or downward esophagoscopically were unsuccessful. An esophagotomy was necessary to extract

the impacted foreign body. In the discussion **Thomas Carmody,** Denver, described a similar case in which a radish became impacted in the esophagus causing a rupture of the esophagus. **James E. Cassidy,** South Bend, Ind., described a case of a marble in the esophagus with removal by a wire snare.

H. L. Kearney, New Orleans, La.: **Fatal Hemorrhage From Perforation of Right Renal Artery by Fish Bone.**—This patient, a man 45 years of age, swallowed a fish bone twenty-four hours prior to being admitted to the hospital. He complained of intense pain between the shoulder blades and had symptoms suggestive of a mediastinitis. The esophagoscopic examination was negative. The pain subsided after the esophagoscopy. Two months later he was readmitted to the hospital because of pain in the back and the abdomen and he was found to be acutely ill. A laparotomy demonstrated a large retroperitoneal hemorrhage and at autopsy a small needlelike fish bone was found in a perforation of the right renal artery. No perforation of the esophagus or of the remainder of the gastrointestinal tract was found to indicate the path of the foreign body but it was felt probable that perforation took place in the duodenum close to the right renal artery.

Herman J. Moersch and **Stuart W. Harrington** (by invitation), Rochester, Minn.: **Benign Tumor of the Esophagus.**—Moersch and Harrington present fifteen cases of benign tumors of the esophagus. These tumors are comparatively rare and are characterized by the fact that they usually reach considerable size before producing symptoms. In over 7,000 post-mortem examinations forty-four benign tumors of the esophagus were found and in none of these cases was there a history of esophageal difficulty. They divide the benign tumors of the esophagus into two types: those arising from the mucosa or submucosa, often called intramural, and those arising from the outer coats of the esophagus, or extramucosal tumors. The former are usually more apt to give symptoms of dysphagia than the latter. They are found more frequently in men than in women and may be encountered at any age, although they are most frequently found after the fourth decade. In the fifteen cases reported, the principal symptom was dysphagia and in several instances the history of regurgitation of the fleshy mass was obtained. Diagnosis is not easy and cannot always be established correctly by roentgen examination, since in the case of large tumors the lesion is frequently confused with that of cardiospasm. An esophagoscopic examination made for diagnosis is likewise not infallible. The error is attributable to the fact that the mucous membrane covering most benign tumors of the esophagus has the same appearance as the esophageal mucosa itself and is so interpreted. In their experience the leiomyoma is the most common type of benign tumor of the esophagus; lipoma, polyp, adenoma, hemangioma, fibroma, and fibrolipoma are the other types of tumors encountered. Treatment was dependent upon the size of the tumor and its location. Tumors with a long pedicle attached to the esophageal introitus were removed with a snare endoscopically. Large tumors were removed by esophagotomy, while small tumors producing few symptoms were considered not to require treatment.

John D. Kernan, New York, N. Y.: **Obstruction of the Right Main Bronchus Due to Congenital Maldevelopment of the Pulmonary Veins in a 4-Month-Old Baby.**—This infant had had attacks of cyanosis from birth, which increased in severity until continuous oxygen was necessary. Physical examination demonstrated a cardiac murmur over the entire chest and chest x-rays showed a widened superior mediastinum. Bronchoscopic examination demonstrated compression of the right main bronchus. On post-mortem examination a greatly dilated right superior vena cava was found, with a persisting left superior vena cava which produced compression of the right main bronchus. There were other extensive cardiovascular anomalies.

Samuel Iglauer, Cincinnati, Ohio: **Spontaneous Mediastinal Emphysema.**—In the case reported, a 3-year-old child suddenly developed crepitant swelling in the neck which soon extended over the face, trunk, and arms. There was no history of illness preceding the onset of the swelling except that of a slight cold. A bronchoscopic examination was done to rule out the presence of a foreign body and none was found. Because of increasing dyspnea, a midline incision was made in the neck through the pretracheal fascia to relieve the mediastinal tension. The child was placed in oxygen and sulfonamide therapy was instituted. Improvement was gradual at first but recovery was complete by the twelfth postoperative day. Iglauer believes that the pathogenesis of this mediastinal emphysema was directly from the alveoli along the sheathes of the pulmonic vessels and into the mediastinum, and that not infrequently this results in pneumothorax.

Arthur E. Hammond, Detroit, Mich.: **Emergency Cervical Mediastinotomy in a Case of Massive Mediastinal and Subcutaneous Emphysema Secondary to Removal of Foreign Body From the Bronchus.**—This case report is that of an 18-month-old infant who had choked on a piece of apple one and one-half hours prior to admission to the hospital. Physical examination and x-ray pictures demonstrated a check-valve obstruction of the left main bronchus. A 5 mm. bronchoscope was used and a portion of the foreign body was extracted with forceps, the remainder being expelled through the bronchoscope during a forced expiration. The infant left the operating room in good condition but twenty minutes later was in extremis due to massive mediastinal and subcutaneous emphysema. The emphysema extended from the head over the entire trunk and involved all four extremities. An immediate cervical mediastinotomy resulted in a release of considerable air under tension and the emphysema gradually disappeared. The infant was discharged from the hospital on the sixteenth postoperative day.

Leighton F. Johnson, Boston, Mass.: **Bilateral Pneumothorax in a Tracheotomized Infant.**—An 8-month-old infant who had been tracheotomized six weeks previously for streptococcic laryngitis at another hospital was admitted to Massachusetts Memorial Hospital for decannulization. An unsuccessful attempt to change the tube required an emergency reincision of the tracheostomy which was followed by a bilateral pneumothorax. Needles were inserted into both pleural cavities immediately, releasing 600 c.c. of air and this was followed by the resumption of normal respiration. X-ray pictures revealed prompt re-expansion of the lung. The infant completely recovered and, following laryngeal dilatation, was decannulated.

Louis H. Clerf, Philadelphia, Pa.: **Tracheopathia Osteoplastica (Osteoma of the Trachea).**—Clerf reviews the previously reported cases of bony tumors of the trachea and adds two cases that have come under his observation. They presented symptoms of hemoptysis and intermittent dyspnea. One patient had a long-standing history of bronchopulmonary and nasal infection whereas the only symptom in the second patient was that of severe recurrent hemoptyses. Bronchoscopic examination revealed ragged nodules and flakes of bone along the tracheal surface and these were found to be connected with the tracheal rings. The posterior wall was free from nodules. Histologic examination of nodules removed with forceps demonstrated them to be composed of bone.

Frederick T. Hill, Waterville, Me.: **Adenoma of the Bronchus, Treated by Coagulation.**—In this case report Hill presents a patient who had been subject to repeated pulmonary infections, supposedly pneumonia. These were complicated by severe attacks of hemoptysis, and bronchoscopic examination demonstrated a tumor of the right lower lobe which proved to be a bronchial adenoma. Therapy has consisted of electrocoagulation which has completely cleared the bronchus and

given complete relief of symptoms. In the discussion **Louis Clerf**, Philadelphia, mentioned a patient who had had an adenoma and has now developed a nodule in the opposite lung, the nature of which has not yet been determined.

Paul H. Holinger, Chicago, Ill., **H. James Hara**, Hinsdale, Ill., and **Edwin F. Hirsch** (by invitation), Chicago, Ill.: **Bronchogenic Carcinoma: An Analysis of 175 Proved Cases.**—A statistical analysis of etiology, symptomatology, pathology, and means of diagnosis is made of this series of 175 proved cases of bronchogenic carcinoma. The most reliable means of establishing a tentative diagnosis was considered to be by x-ray, while bronchoscopy was found to be the most reliable means of establishing a positive diagnosis. In 8 per cent of the cases more than one year elapsed between the initial symptoms and bronchoscopy. In 42 per cent six months to one year elapsed, and in the remaining 50 per cent less than six months elapsed. In 78 per cent of cases a positive bronchoscopic biopsy was obtained. The carcinoma was found on the right side in 111 of the cases and on the left in 60, while in 4 cases it was bilateral. In character, 64 per cent of the tumors were squamous cell, 17 per cent small round cell carcinomas, 13 per cent anaplastic carcinoma, and 6 per cent adenocarcinoma. The technique of bronchoscopic biopsy and criteria of operability are discussed. Therapy is considered surgical in every possible instance, but in cases unsuitable for surgery palliative irradiation or bronchoscopically applied radium or radon is mentioned.

F. W. Davison, Danville, Pa.: **Does Chronic Sinusitis Cause Bronchiectasis?** Davison points out that while chronic sinusitis and bronchiectasis are often found in the same patient, this does not mean that one infection is the cause of the other. Of fifty patients with bronchiectasis, Davison found that 72 per cent developed their bronchiectasis during the first decade of life, 74 per cent of these tracing the onset of their chronic cough to an acute bronchopulmonary infection. Davison showed that mucosal edema of 1 mm. in a 6 mm. bronchus reduced the size of the lumen 42 per cent, while the same amount of edema reduced a 3 mm. bronchial lumen of a child to 11 per cent of its original airway. It was felt that mucosal edema was probably the chief factor responsible for the atelectasis which led to the development of the bronchiectasis. He attributes this mucosal edema to an allergic or hypersensitive state and noted that the allergic or hypersensitive state was an etiologic factor of bronchiectasis in 80 per cent of his series of fifty patients with bronchiectasis. In comparing these patients with fifty patients with sinusitis, Davison notes that the patients with sinusitis and bronchiectasis are twice as numerous when an allergic factor can be demonstrated. He noted that thirty-three patients who had both sinusitis and bronchiectasis were of the allergic type, suggesting that excessive mucosal edema found in these hypersensitive individuals predisposed them to the development of sinusitis as well as to development of bronchiectasis.

Chevalier L. Jackson and Charles M. Norris (by invitation), Philadelphia, Pa.: **Anatomy of the Bronchial Tree and Lungs With a Simple Nomenclature.**—This presentation was an animated motion picture film in color correlating the endoscopic landmarks of the lobar and segmental bronchi with their corresponding lobes and segments. The positions and relations as well as the relative size and importance of various lobes and segments were shown, together with a diagrammatic representation of the endoscopic picture at various levels in the tracheobronchial tree. The nomenclature included terms selected on a basis of topographical relationship and conserved the clinical names of "apical" and "basal" for segments of the apex and base of the lung respectively. The lungs were subdivided according to their bronchial distribution with each lobar segmental bronchus taking the name of the lobe or segment to which it corresponded. In the discussion, **Herman Moersch**, Rochester, Minn., suggested the adoption of the uniform nomenclature among the various groups interested in this specialty.

Book Reviews

Industrial Ophthalmology. By Hedwig S. Kuhn, M.D. Ed. 1, pp. 294, with 114 illustrations. St. Louis, 1944, The C. V. Mosby Company. $6.50.

Dr. Kuhn has made a splendid contribution to ophthalmic literature. She has at last given us a concise and well-illustrated monograph that can and will be accepted as an authoritative reference book by all interested in industrial ophthalmology. She has added dignity and meaning to the term Industrial Ophthalmologist, and the term Company Oculist should soon vanish.

The chapter on Visual Testing in Industry gives a plan of placing employees in industry where their visual skills indicate they should be. She describes in detail the use of the new orthorater visual screening tests in industry. This is an instrument which can be operated by a technician, and the records kept by a punch-card system. This enables the ophthalmologist to pick out the employees with glaring visual defects without laboriously examining every employee. Other tests are discussed and their advantages pointed out.

The chapter on Correction of Visual Defects, as they relate to the patient's job, should interest all ophthalmologists because it presents many practical applications which can be used in everyday practice as well as in industry.

The chapter on Industrial Eye Injuries Caused by Solid Bodies was contributed by Dr. Albert C. Snell of Rochester, N. Y. It is full, yet concise and to the point, giving many of Dr. Snell's common sense rules for handling the various types of ocular injuries. To those of us who know Dr. Snell, we realize that he has no peer in this field, having devoted many years of a long and useful life to this subject, both as a teacher and a practitioner.

The chapter on Goggles and Eye Protection is complete and well illustrated. It gives a method with concrete suggestions as to how a successful goggle plan can be instituted and operated for the protection of eyes in large industrial plants.

The last chapter is devoted largely to recent developments, such as "flash burns" and epidemic keratoconjunctivitis, with suggestions as to management and treatment. The section on Illumination should be read and reread both by labor and management, as well as by the ophthalmologist.

Books Received

The receipt of books is acknowledged in this section and this treatment must be regarded as sufficient acknowledgement of the courtesy of the senders. Selections will be made for more extensive review dictated by the interests of our readers and as space permits.

VASCULAR RESPONSES IN THE EXTREMITIES OF MAN IN HEALTH AND DISEASE. By David I. Abramson, M.D., Captain, A. M. C., Cardiovascular Research, May Institute for Medical Research of the Jewish Hospital, Cincinnati. Cloth. Price $5.00. Pp. 412, with 52 illustrations. Chicago, 1944, University of Chicago Press.

TROPICAL NURSING—A HANDBOOK FOR NURSES AND OTHERS GOING ABROAD. By A. L. Gregg, M.A., M.D., Hospital for Tropical Diseases, London Westminster Hospital Medical School. Cloth. Price $3.00. Pp. 185, no illustrations. New York, 1944, Philosophical Library, Inc.

VIRUS DISEASES IN MAN, ANIMAL, AND PLANT. By Gustav Seifert. Cloth. Price $5.00. Pp. 332, no illustrations. New York, 1944, Philosophical Library, Inc.

SMALL COMMUNITY HOSPITALS. By Henry J. Southmayd, Director, Division of Rural Hospitals, The Commonwealth Fund, New York City; Geddes Smith, Associate. Cloth. Price $2.00. Pp. 182, with 4 illustrations. New York, 1944, Commonwealth Fund.

PRACTICAL MALARIA CONTROL. By Carl E. M. Gunther, M.D., Field Medical Officer, Australian Medical Corps. Cloth. Price $2.50. Pp. 91, no illustrations. New York, 1944. Philosophical Library, Inc.

SURGICAL CLINICS OF NORTH AMERICA, REPARATIVE SURGERY. By many contributors. Cloth. Pp. 490, with 141 illustrations. Philadelphia, 1944, W. B. Saunders Company.

THE AMERICAN ILLUSTRATED MEDICAL DICTIONARY. By W. A. Newman Dorland, A.M., M.D., F.A.C.S., Lieutenant-Colonel, M. R. C., U. S. Army, in collaboration with E. C. L. Miller, M.D., Medical College of Virginia. Leather. Price $7.00, plain; $7.50, thumb-indexed. Pp. 1668, with 885 illustrations. Philadelphia, 1944, W. B. Saunders Company.

MINOR SURGERY. By various authors. Edited by Humphry Rolleston and Alan Monerieff. Cloth. Price $5.00. Pp. 174 with 30 illustrations. New York, 1944, Philosophical Library, Inc.

TECHNIQUE IN TRAUMA. By Fraser B. Gurd, M.D., C.M., and F. Douglas Ackman, M.D., C. M., Montreal General Hospital and MacGill University. Cloth. Price $2.00. Pp. 68, with 3 illustrations. Philadelphia, 1944, J. B. Lippincott Company.

TREATMENT OF PEPTIC ULCER. By George J. Heuer, M.C., Professor of Surgery, Cornell University Medical College, and Surgeon-in-Chief of New York Hospital. Cloth. Price $3.00. Pp. 118, no illustrations. Philadelphia, 1944, Barbara Whitney Henry Fund, J. B. Lippincott Company.

DENTAL TREATMENT OF MAXILLO-FACIAL INJURIES. By W. Kelsey Fry, M.C., M.R.C.S., L.R.C.P., Consulting Dental Surgeon to the R. A. F., Consulting Dental Surgeon to Ministry of Health and to Guy's Hospital; and others. Cloth. Price $6.50. Pp. 434, no illustrations. Philadelphia, 1944, J. B. Lippincott Company.

INFECTIONS OF THE PERITONEUM. By Bernhard Steinberg, M.D., Director of Toledo Hospital Institute of Medical Research; Past Fellow of National Research Council; Former Crile Research Fellow, Western Reserve University. Cloth. Pp. 454, with 45 illustrations. New York, 1944, Paul B. Hoeber, Inc.

INTRAVENOUS ANESTHESIA. By R. Charles Adams, M.D., C.M., M.S. (Anesthesiology), Associate in Section on Anesthesiology, Mayo Clinic; Instructor in Anesthesiology, Mayo Foundation. Cloth. Price $12.00. Pp. 663, with 73 illustrations. New York, 1944, P. B. Hoeber, Inc.

THE NEUROSURGICAL PATIENT. By Carl W. Rand, Professor of Neurological Surgery, University of Southern California, School of Medicine, Los Angeles, Calif. Cloth. Price $4.00. Pp. 576, with 121 illustrations. Springfield, Ill., 1944. Charles C Thomas, Publisher.

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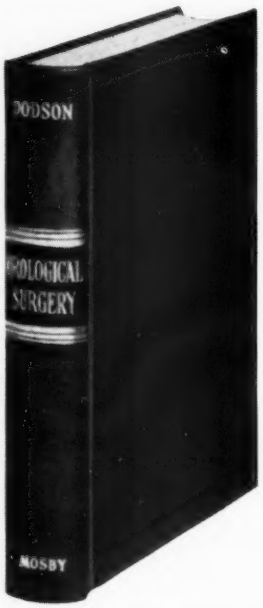

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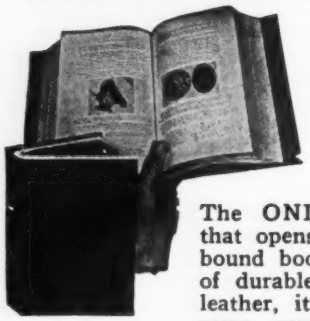

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The two previous editions of this book were highly popular with the profession in America, not merely because coming from the famous Edinburgh school, but because written for general surgeons, by a general surgeon who has risen to international distinction for the excellence of his teaching and practice of orthopedic surgery. The Edinburgh Medical School maintains the tradition that a surgical specialty is only a branch of general surgery, and that to become a good specialist one must first be a good general surgeon. It is the broad viewpoint and wide experience of the general surgeon which is continually reflected in the pages of this book. An approach which gives a clearer grasp of the problems involved in orthopedic work and greater resourcefulness and skill in treatment.

This wartime edition has been rewritten, revised and produced under many difficulties, but every page and chapter has been gone over carefully and many new ideas incorporated, both from the author's own recent experience and that of others. Many operations no longer considered useful have been deleted and where prudent a choice of procedure is indicated. Among the sections extensively rewritten are those on Circulatory Disturbances, Affections of the Back, Knee, Shoulder and Foot, and Infections of the Hand.

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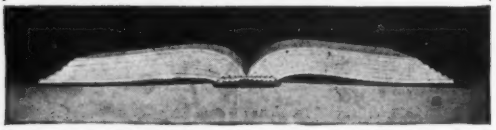

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